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PATHOPHYSIOLOGY OF CARDIOPULMONARY BYPASS

(Extracorporeal Circulation)

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With the rapid progress in surgical correction of cardiac defects it became quite apparent that the optimum conditions for operating in the heart and great vessels were those in which a "dry" or bloodless field could be achieved. Within the past ten years and indeed at this moment, rapid strides are being made in achieving this goal. A "clean" operative field in the heart necessarily means that this vital organ must be mechanically bypassed. To achieve an apparatus which would duplicate this function, the blood not only must be mechanically pumped, but also mechanically oxygenated. A heart-lung machine outside of the body to perform its major function must duplicate the normal physiologic function of the heart and the lungs.

The criteria for a satisfactory extracorporeal machine, therefore, are:

1. The ability to maintain adequate systemic blood pressure.
2. To allow for normal gas exchange: O_2, CO_2.
3. To preserve the natural blood elements.
4. To sustain normal chemical status of the body, and thus normal metabolism.

The recent experience of bypass procedures has allowed many heretofore impossible procedures to be done. For example, to work on a mitral valve or on a ventricular septal defect under direct vision is now a reality with increasing success. That such successes are growing in number is not only due to improved surgical methods and understanding of basic pathological defects, but in no small measure to the perfection of the artificial heart-lung apparatus.

Some of the problems which plagued early workers in this field were the pathologic changes in the normal physiology which take place simply due to the "machine." What happens to the blood elements, plasma, electrolytes, pH, buffer systems, vascular system, central nervous system, O_2 and CO_2 exchange when the blood is circulated and oxygenated artificially?

Before answering this question, we must ask ourselves three basic ones. What are the essential requirements for (1) a blood pump, (2) a blood oxygenator, and (3) an adequate perfusion.

An ideal pump should have these basic characteristics. There should be free flow

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through adequate orifices with minimal restrictive areas. The pump should be simple to operate and there should be no trauma to the blood; surfaces should be smooth (siliconized) and the propelling mechanism should be smooth. The rates of flow should be easily variable and controlled. The pumps in use today have proven themselves and are performing well. Mechanical refinements will constantly be made until the ideal pump is attained.

CRITERIA FOR IDEAL OXYGENATOR

What are the requirements for an ideal oxygenator or, more correctly, a device for blood gas exchange?

It should provide for maintaining normal oxygen saturation and carbon dioxide levels in the blood delivered to the patient. Different approaches have been made. Some clinics use a membrane oxygenator which allows the gas exchanges to take place across a membrane (such as teflon or polyethylene). The blood and gas are separated and this closely duplicates the normal lung for which it is a substitute.

Other clinics use the method of blood and gas direct interface; that is, the blood in thin layers is exposed to an O_2 medium where the blood becomes saturated with oxygen and gives off the CO_2. Screen, disc, and bubble type oxygenators use this method successfully.

The ideal oxygenator should, therefore:

1. Maintain normal O_2 and CO_2 relationships.
2. Be kept at or near body temperatures, or varied to assume the temperature desired for a specific perfusion.
3. Produce no turbulence to the blood (and probably have no moving parts).
4. Not change blood volume by adding or removing water from the blood stream.
5. Need little or no priming volume.
6. Be easily assembled, cleaned and sterilized.
7. Probably avoid direct blood and gas interface, but carry on the gas exchange across a membrane most closely simulating a normal lung.

A diversity of types of equipment is today being used with success.

ADEQUACY OF PERFUSION

The heart-lung machines can deliver varying rates of flow from 500 cc. to 5000 or 6000 cc/min. But what is an adequate perfusion? A simple answer would be: an adequate total body perfusion is one which allows careful, deliberate correction of a pathological defect in the bloodless heart with recovery of the patient. Experimental and clinical evidence has shown that a rate of 2.3 liters/square meter of body surface/min. is physiologic. (This roughly approximates 75 cc/min/kg body weight). Such an artificial perfusion would give an aortic blood pressure of about 100 mm. Hg (systolic) and a venous pressure of 10-20 mm. Hg, arterial pH would be maintained at between 7.30-7.40, arterial oxygen saturation of 95-98% (100-250 mm. Hg pO_2) and venous saturation of 70-80% (pCO_2=30-40 mm. Hg) would be established.

When perfusion is adequate for body maintenance, the changes in chemistry of the blood will be minimal. The acid base balance will be fairly well maintained. However, with prolonged and inadequate perfusion, the metabolic changes (which ideally would be absent) become evident. Na^+ and Cl^- show minor changes. K^+ may fall slightly but the pH may drop toward the acidotic side. For the first 30 min. as a rule pH will maintain itself. The buffer system of the blood maintains equilibrium in the acid base relationships until retained CO_2 and accumulated metabolic acids (lactic, pyruvic) will lower the pH.

In practice, before the patient is placed on bypass of the circulation, the anesthetist creates a respiratory alkalosis by hyperventilation — this plus addition of $NaHCO_3$ and sodium lactate solution tends to combat developing acidosis in patients undergoing prolonged procedures. When a successful extracorporeal technique has been used and a curative surgical result is obtained, the patient, as a rule, will be able to spontaneously handle the lowered pH. When the lowered pH is progressive, the deterioration of the patient is comparable to hypovolemic shock.

A problem which may occur is in the stored blood. In the stored donor blood, after four hours, there is a drop in pH. This is due to glycolysis. The priming volume of such donor blood may exceed the total blood volume of a small child and, in such a case, the accumulation of acid will be significant in lowering the pH of the patient. Therefore, freshly drawn donor blood is best.

MANAGEMENT OF CLOTTING MECHANISM

Coagulation problems one faces with the use of "the machine" are usually well managed. With adequate use of heparin, the fibrinogen, prothrombin and thrombocyte content of the blood will be controlled. Inadequate heparinization will deplete fibrinogen, prothrombin and platelets by the formation of small clots. It is, therefore, best to use freshly drawn donor blood, adequately heparinized. The patient also receives heparin in doses of 1.5 mgm/kg. repeated at intervals of 30-45 min. during the bypass.

After a prolonged run, fibrinolytic titres in the blood may rise to combat formation of new fibrinogen. Lack of fibrinogen will result in excessive bleeding. This is treated by I.V. injection of fibrinogen (6-12 gm.). The decrease in number of thrombocytes progresses with duration of bypass. The heparin is neutralized by protamine after the patient has been decannulated and the extracorporeal unit is removed.

EFFECTS ON THE BRAIN

Throughout extracorporeal circulation, the organ of critical importance is the brain. With proper and effective bypass, there is no apparent ill effect on the nervous tissue. Fifteen percent of the total body flow is cerebral flow, and this corresponds roughly to 50 cc. of blood/100 gm. of brain/minute. The damage which might occur to the brain follows decreased flow of blood through the brain, or physicochemical defects within the blood which reaches the brain. The cerebrovascular bed is quite sensitive to O_2 and CO_2 tensions. The volume of blood passing through this bed is proportional to the arterial blood pressure and inversely proportional to cerebrovascular resistance. With decrease in O_2 tension and increase in CO_2 tension, the vascular resistance drops and, conversely, with increase in O_2 tension and decrease in CO_2 tension, the vascular resistance increases.

A drop in body temperature (such as in the case of induced hypothermia) also causes an increase in cerebrovascular resistance. Brain tissue can survive only three to four minutes without circulation, i.e., without O_2. There are also dangers of an excess of O_2 in the blood reaching the brain. The question of oxygen intoxication is a debatable point. The possibility of supersaturation of the blood plasma with O_2 is a very real and practical problem. Since O_2 is most soluble in blood at low temperatures, the danger arises when blood is circulated through the body at its normal temperature. When cooler blood going through the machine is exposed to high O_2 concentrations some of the O_2 may go into solution. This cooled blood, when it goes through the body at higher temperatures, releases O_2 in the form of bubbles. Bubble emboli in the brain can cause irreversible damage and death.

Other qualities of the blood affecting the cerebrovascular flow are the electrolytes, metabolic products and foreign materials. The foreign materials (particulate matter, fibrin clots, silicone emboli, pieces of tissue released during the surgery) are filtered out of the system before they produce their ill effects.

Brain damage may become evident during the perfusion or in the postoperative period. During perfusion, if one uses the electroencephalogram, abnormalities may be monitored. From a practical point of view, size of pupils and monitored arterial blood pressure are important. Widely dilated pupils which do not reverse are an omen of cortical damage. In the postoperative period, lethargy, coma, convulsions and other focal neurologic signs point to brain injury.

EFFECTS ON KIDNEYS AND LUNGS

Renal function can be adequately supported if the perfusion is anything above the minimum of 35 cc/kg of body weight. A good total body perfusion will give no renal problems.

The effect of extracorporeal circulation on lungs also is minimal when the bypass works well. With inadequate perfusion, there is evidence of a breakdown of the elastic fibers in alveoli, leading to damage of the pulmonary alveolar membrane.

BLOOD VOLUME ALTERATIONS

Alteration in blood volume during total body perfusion is not well understood. During prolonged procedures blood is probably sequestered in vascular beds outside of the circulatory blood stream. The method of weighing the patient directly after surgery does not, therefore, give one an accurate picture of the effective circulatory blood volume. Estimating and replacing blood loss has proven to be inaccurate. In spite of constant flow rates and monitoring arterial and venous pressure during perfusion, patients have been found to be hypovolemic at the close of a procedure. The most accurate and reliable method is to measure blood volume using rapid techniques with radioisotopes. Volume measuring machines which give the answers within fifteen minutes are now available.

The scope of this discussion does not include the great advances in total body hypothermia, local hypothermia and profound hypothermia, nor shall we discuss the physiologic implications of induced cardiac asystole and the associated myocardial metabolic studies. These are adjuncts to the use of mechanical extracorporeal circulation.

The past decade has been exciting and fruitful in the development of the heart-lung machine and its uses. Basic physiologic facts are bearing fruit and being applied to clinical use in the extra corporeal circulation techniques. Certainly, many refinements are in store but the "ball is rolling" and a look to the future fires one's imagination.

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STRUMA LYMPHOMATOSA

A Clinicopathologic Case Study and An Evaluation of Recent Progress

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INTRODUCTION

Until almost a decade ago it was generally accepted that struma lymphomatosa was relatively rare, that it accounted for approximately 1% of surgical thyroidectomy specimens, that laboratory procedures were of little value in differential diagnosis, that almost all cases were diagnosed only after pathologic study of the operatively excised thyroid mass, that pathologic studies suggested an infectious etiology and that surgical excision was the treatment of choice.[9] None of these statements appear valid today.

Since the disease is now common and is apparently increasing in frequency,[3] since modern diagnostic techniques permit reasonable accuracy in clinical diagnosis,[5,6,7,8] since many thyroidologists today elect conservative therapy with desiccated thyroid in preference to surgery,[1,7,8] since there have been major advances in our fundamental scientific knowledge of this subject,[6,10] and since much of this new knowledge is clinically applicable, our available material is discussed in the light of these recent advances. Special emphasis is placed on the current status of the role of auto-immunity and the significance of newly available laboratory diagnostic procedures.

Our definition of struma lymphomatosa is based upon morphologic features described and illustrated in the presentation of data.

To avoid terminologic confusion from the onset, it should be clearly stated that the term struma lymphomatosa is regarded as a synonym for lymphocytic thyroiditis, lymphocytic goiter, Hashimoto's disease, chronic thyroiditis and autoimmune thyroiditis. The term does not include acute or suppurative thyroiditis, Riedel's struma, or De Quervain's granulomatous pseudotuberculoid subacute thyroiditis.

METHOD OF STUDY

In order to compare and contrast the clinical experience at Mount Sinai Hospital with current reports, we have re-

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viewed all thyroid surgical specimens and slides acquired by The Department of Pathology for a corresponding 15 month period at the beginning of each of four decades from 1930 to 1960. Clinical data were collected only for the cases diagnosed during 1960-1961 because modern diagnostic technics were not available during previous periods.

PRESENTATION OF DATA

The data obtained from the review of the charts and re-examination of the pathologic material is summarized in Tables 1 to 3 and illustrated in Figures 1 to 6.

Table 1.

COMPARATIVE INCIDENCE OF STRUMA LYMPHOMATOSA

Total Number Path. Lab. Thyroidectomy Specimens		Struma Lymphomatosa No. of Cases	%
1930-1931	68	0	0%
1940-1941	63	3	4.8%
1950-1951	84	5	6.0%
1960-1961	59	9	15.3%

N.B.: Each collection period was of 15 months duration.

No case of struma lymphomatosa was included among 68 thyroidectomies performed in 1930-1931. During 1940-1941 three cases were confirmed in a series of 63 thyroidectomies (4.8%). During 1950-1951 five cases were confirmed in a series of 84 thyroidectomies (6%). During a recent fifteen month period in 1960-1961, nine cases were pathologically confirmed in a series of 59 thyroidectomies (15.3%).

All of the patients were females ranging in age from 27 to 50 with an average age of 39. All but one patient presented with a neck mass which had been present for from 3 weeks to 18 years. A neck mass was first noted in one patient during the initial routine physical examination. Approximately half of the patients noted a recent increase in size of the mass. None complained of "sore throat," neck pain or fever. Mild difficulty in swallowing was present in 4 of 9 cases.

No patient was demonstrably hyperthyroid by either clinical or laboratory criteria. No patient was clinically myxedematous. One patient had laboratory evidence of marked thyroid hypofunction. When performed, the B.M.R. was usually low.

A neck mass varying from 2 to 6 cms. was usually easily palpable. No single case presented a uniformly diffuse enlargement. No case in this series was tender. The diffuseness and symmetry stressed in the literature were not evident in this series. The mass was usually asymmetrical, with a prominence of one or the other lobe or isthmus, was sometimes suggestively nodose or bosselated, varied from firm to hard, was usually freely movable and was not adherent in any of these cases.

The recorded laboratory data in our cases is summarized in Table 2. Four antibody titer studies were done; in only one case did the titer reach 1/640 with the sensitized tanned red cell agglutination test.

The correct clinical diagnosis was not established with certainty in any case preoperatively but was suggested as a highly probable diagnosis twice. The usual preoperative diagnosis was adenomatous goiter or adenoma. Very firm masses were suspected as possible carcinomas.

The gross appearance may be well-nigh diagnostic (see Figures 1 and 2). The microscopic changes are illustrated in Figures 3 to 6. The most obvious microscopic change is the non-suppurative, mononucleated, predominantly lymphocytic, inflammatory infiltrate, which is usually diffuse and usually associated with focal lymphoid follicle production. The more important alterations, however, are parenchymal. There is mild to marked follicular and epithelial change which varies over a wide gamut. One may note early degenerative cellular changes, focal cellular necrosis, disruption of the follicular reticulin, disruption of follicular continuity and apparent leakage of colloid into the interacinar stroma. This type of alteration, which is not always found, is presumed by

TABLE 2. SYMPTOMS, SIGNS AND LAB DATA

CASE NO.	1	2	3	4	5	6	7	8	9
Age	28	41	45	36	27	29	45	46	50
-SYMPTOMS-									
Neck Mass	+ (5yrs)	+ (3wks)	+ (not noticed by patient)	18 yrs.	+ (4mo.)	+ (dur.?)	+ (2yrs)	+ (5yrs)	+ (1mo.)
Sudden increase size.	+ (1yr)	+	NS	+	+ (2wks)	NS	+ (2mos.)	0	0
"Sore throat"	0	0	NS	(hoarse-ness)	0	0	0	0	(hoarse-ness)
Pain	NS	0	NS	0	0	0	0	0	0
Pressure Symptoms									
Breathing	0	NS	NS	0	0	0	0	0	+
Swallowing	+	+	NS	+	0	0	0	0	+
-SIGNS-									
Size of mass	NS	NS	NS	NS	6 x 6 cm.	"large"	3 x 3 cm.	2 cm.	NS
Location of mass	Diffuse	Diffuse	Left lobe & isthmus	Pyram.lobe & isthmus	Right	Right	Left	Left & pyram.	Bilateral
Nodularity	0	NS	+	+	+	+	+	+	+
Consistency	NS	Firm	Not hard	Firm	Firm	Firm	NS	Hard	Hard
Mobility	NS	NS	Mobile	Mobile	Mobile	NS	NS	Mobile	Mobile
Adherence	NS	0	NS	0	0	NS	NS	0	0
Tenderness	NS	0	+	0	0	0	0	0	0
-LAB DATA-									
BMR	ND	-25% -21%	-3% -1%	ND	ND	-7% -11%	ND	-15% -13%	ND
PBI	ND	2.1	3.9	ND	ND	5.9	ND	ND	ND
RAI Uptake	ND	ND	32%	ND	ND	ND	ND	ND	ND
Cholesterol	101	264	ND	ND	173	ND	ND	ND	ND
Antibody titer	Low	Low	ND	ND	ND	ND	ND	Low	1/640

+ = Symptom or Sign Present
0 = Symptom or Sign Absent
NS = No Statement Available
ND = Not Done

TABLE 3. PATHOLOGIC FEATURES

CASE NO.	1	2	3	4	5	6	7	8	9
-GENERAL FEATURES-									
Weight	12 gms.	NS	26 gms.	20 gms.	26 gms.	10 gms.	NS	14 gms.	NS
Size	R-4x3x2 L-3.5x2.5 x1	a)6.5x3x1.7 b)2x2x1	5.4x3.3 x1.3	a)6.5x4x3 b)2.5	8.5x4.5x3	a)5x1.5x1.5 b)2.5x2x1	R-3x2x1 L-4x2x1	NS	R-6x5x3 L-5x3.5x3
Side	R & L	R & Isthmus	R & L & isthmus	Pyrm.lobe & isthmus	R	R & isthmus	R & L	L & isthmus	R & L
-EXTERNAL SURFACE-									
Smooth	+	0	0	0	0	0	0	0	0
Lobular or nodular	0	+	+	+	+	+	+	+	+
-CUT SURFACE-									
Color	Red with gray-white mottling	Grayish-white	Grayish-white	Brownish-tan	Grayish-white	Grayish-tan	Yellow-pink	Tan-pink	Pink-white
Nodulation	0	Fine nodularity	Variable-to 2 cm.	NS	Fine nodularity	Fine	Fine	Fine	Fine
Consistency	Soft	Hard	Firm	Firm	Hard	Firm	Firm	Soft	Hard
-HISTOPATHOLOGY-									
Follicular preservation	85%	75-85%	25-50%	50%	10%	50%	85%	60%	25-50%
Acinar epithelial eosinophilia	Slight	Moderate	Moderate	Slight	Slight	Slight	Insignificant	Slight	Slight
Lumen									
Colloid	Almost normal	Marked depletion	Marked depletion	Moderate depletion	Marked depletion	Light, pale	Almost normal	Almost normal	Marked depletion
Desquamated cells	0	+++	+	Few	+	Occas.	0	Occas.	Occas.
Cellular infiltrate									
Diffuse lymphocytic	Slight	++	++	++	++	+	Slight	++	++
Follicular	+	Slight	+	+	++	++	+	Slight	+
Extent	Mild	Marked	Moderate	Moderate	Extensive	Marked	Mild	Moderate	Moderate
Plasma cells	Rare	Moderate	Moderate	Rare	Moderate	Few	Few	Few	Moderate
Granulomatous foci	0	0	0	0	Few	0	0	0	0
Fibrosis	0	Slight	Considerable	Sparse	Moderate	Moderate	Slight	Slight	Moderate

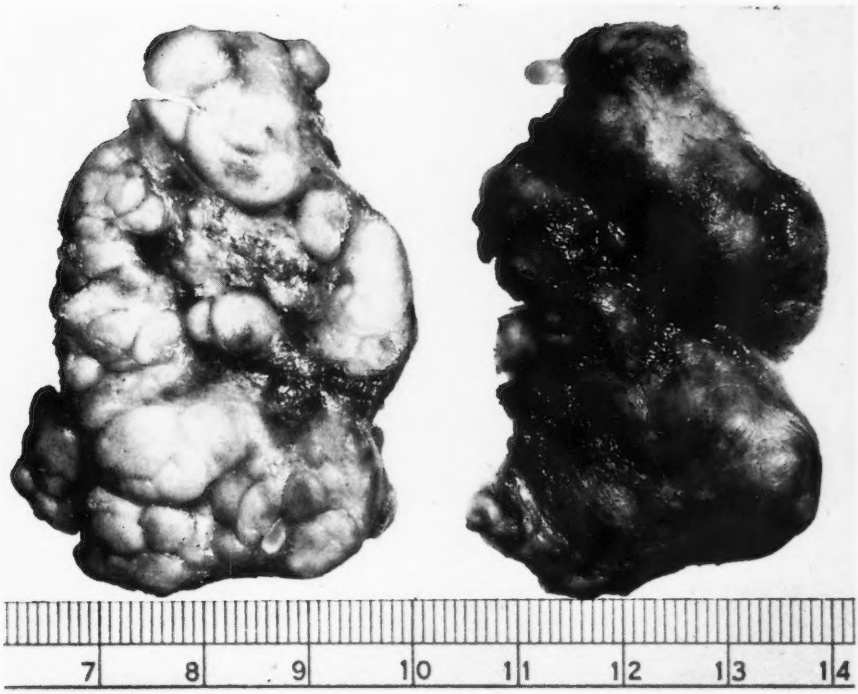


Figure 1.

Gross appearance. External surface on right. Note irregular bosselation rather than a smooth surfaced, diffuse enlargement. Cut surface on left. Note pseudolobular nodules, easily palpable, originally gray-tan in color, separated by connective tissue.

some to be the primary phase of the pathologic pattern but this thesis has not yet been conclusively established.

There is often widespread "exhaustion atrophy" of epithelium with plump, deeply eosinophilic epithelium, which was once held by some to distinguish "true Hashimoto's syndrome" from the remainder of the group of "chronic thyroiditis." Often the follicles are crowded together with small or tiny lumina containing sparse or no colloid. The extent of follicle preservation or disruption varies widely. The follicular epithelium may vary from atropic to focally hyperplastic. Lumina commonly contain desquamated epithelial cells and/or macrophages. The degree of stromal fibrosis also varies widely from thin septa which do not clearly demarcate lobules to dense bands which grossly outline nodules. It appears noteworthy that the two cases with a neck mass of long duration (5 and 18 years) had only slight to moderate fibrosis. Fibrosis is not necessarily irreversible or progressive. Widespread dense fibrosis is rare and is **not** synonymous with Riedel's struma. The latter term is usually reserved for a syndrome involving dense ligneous adhesion to the trachea and adjacent tissue which requires sharp surgical dissection for removal.

Plasma cells may be present in the cellular infiltrate either sparsely or in large numbers. We cannot correlate the presence of plasma cells with available antibody titer studies. An occasional giant cell and even a small granulomatous focus was rarely found but no case presented a problem of differential diagnosis from De Quervain's pseudotuberculoid granulomatous subacute thyroiditis.

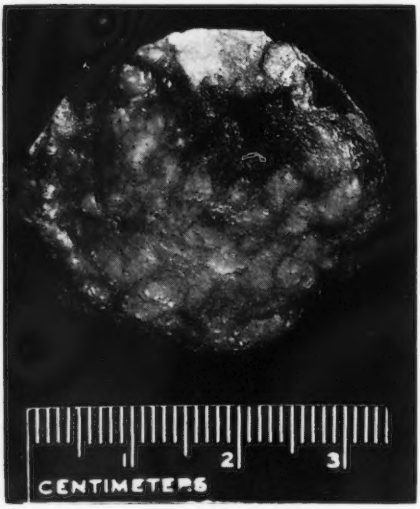


Figure 2.

Gross appearance of cut surface of another case which is smooth but studded by ball-shaped lymphocytic masses, more easily seen than felt. This type of case may present clinically as a smooth surfaced, diffuse enlargement.

Frozen section diagnosis was requested in only 3 cases. One needle biopsy was done in the operating room.

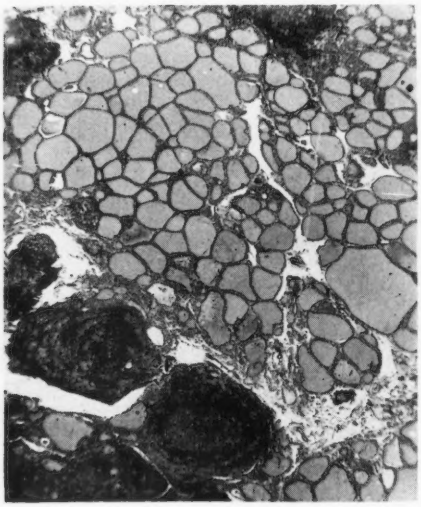
Originally, we expected to correlate clinical and morphologic features. It might be expected that such features as size, duration of lesion, hypothyroidism, tenderness, etc., could be correlated with the degree of follicular preservation, extent of cellular infiltration, amount of fibrous tissue, etc. No such simple correlation is evident in this material.

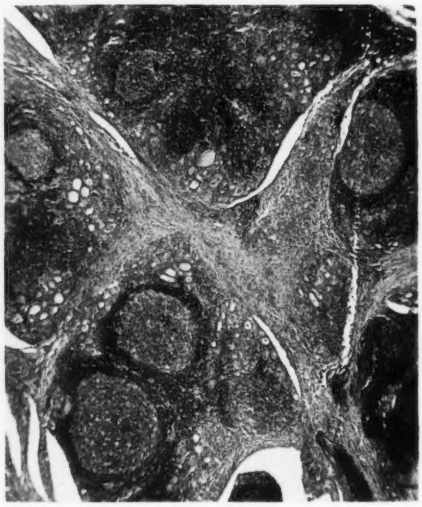
Our material includes no case of carcinoma associated with struma lymphomatosa.

DISCUSSION

Several authors have recently stressed the high and increasing incidence of struma lymphomatosa.[3] Our current incidence figure of 15.3% is higher than most reported and has increased significantly since 1930.

The frequency of the disease,[3] the availability of newer diagnostic procedures,[1,6,7,8] the vigorous contention of most recent authors that surgical excision is





Figures 3 and 4.

Low-power microscopic sections (original magnification 25X). Note that lymphoid follicles with germinal centers are of similar size in Figures 3 and 4. Figure 3 demonstrates preservation of most acini, cuboidal lining epithelium, normal colloid, minimal diffuse infiltrate, multiple lymphoid follicles, and no fibrosis. Figure 4 includes no normal acini, occasional small, distorted acini empty of colloid, diffuse and follicular lymphocytic infiltrate and dense fibrous connective tissue septa.

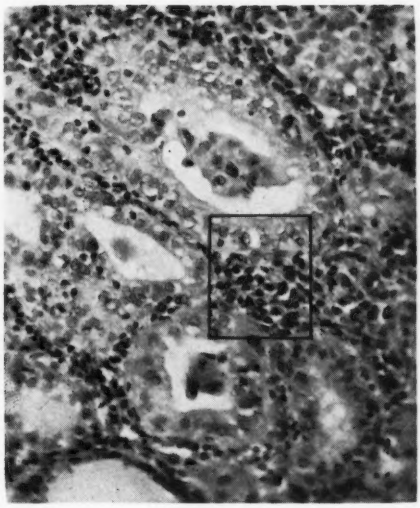


Figure 5.
Mid-power microscopic section (original magnification 240X). Acini lined by columnar epithelium, empty of colloid but containing macrophages, with diffuse, non-follicular, mononucleated cellular interstitial infiltrate.

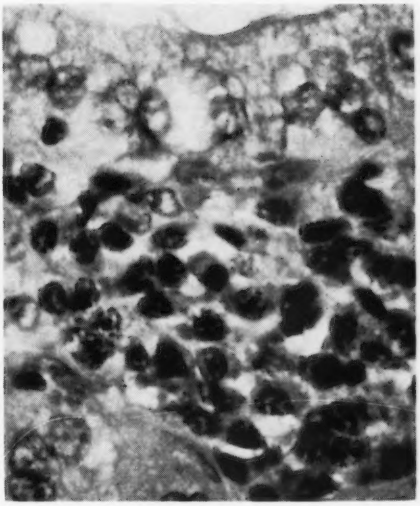


Figure 6.
Oil immersion view (original magnification 1000X). Field with plasma cells, enlarged from the right central area of Figure 5.

unnecessary,[4,7,8] together with the fact that most cases in average clinical practice are preoperatively diagnosed as nontoxic goiter,[5] suggests the need for and potential value of more painstaking attempts at differential diagnosis.

The development of new diagnostic laboratory procedures is inextricably intertwined with the study of the etiology and pathogenesis of the disease.[6,7,8,10]

The inability to find a causative microbiological agent, the lack of an acute suppurative reaction, the inability to transmit the disease and other factors cast doubt on the probability of an infectious etiology many years ago.

The cytologic alterations, the cellular eosinophilia, evidence of exhaustion atrophy, and the associated compensatory hyperplasia and hypertrophy of thyroid cells led to the concept of primary thyroid failure with compensatory thyroid enlargement in opposition to the concept of a true thyroiditis.[7,8] The concept of primary thyroid failure naturally led to emphasis on diagnostic studies of thyroid function (hypofunction) outlined in Tables 4 and 5.

Experiments, studies and concepts developed by Witebsky, et al.[10] and Doniach and Roitt[6] in 1956 have revolutionized subsequent progress in this field. Witebsky et al. demonstrated that when half a rabbit thyroid was removed, homogenized, and administered as an antigenic substance with Freund's adjuvant back into the same rabbit, the remaining half of the gland developed a lesion pathologically similar to struma lymphomatosa. Further studies demonstrated the presence of circulating anti-thyroid antibodies in the serum of the rabbit. Almost simultaneously Doniach and Roitt published their data on abnormal serum globulins and the findings of thyroid autoantibodies in struma lymphomatosa in man. This work suggested an auto-immune mechanism for struma lymphomatosa, opened a vast field of experimental study and led to the use of diagnostic tests based on immunologic technics. Although many aspects of the problem require additional study, there is now general agreement that auto-immune mechanisms are involved in the etiology and pathogenesis of struma lymphomatosa.

Originally, it was suspected that primary thyroid follicular disruption of undetermined cause resulted in the liberation of thyroglobulin. Once outside the follicles, thyroglobulin can act as an antigen to incite the production of antithyroglobulin antibodies which may be demonstrated in the circulating blood. Originally, it was thought that such circulating anti-thyroglobulin antibodies were responsible for further follicular disruption and inflammatory reaction. More recent work, however, has shown that cytotoxic antibodies which destroy thyroid cells in tissue culture and which are distinct from other circulating antibodies are more probably of etiologic and pathogenetic significance. The circulating antibodies which are usually studied clinically are probably only an indirect index of more significant cytotoxic antibodies.

Basic data concerning some known antibodies is included in Table 6.

In clinical laboratory practice it is simplest to test for the thyroglobulin-antithyroglobulin system by the sensitized tanned red blood cell technic. This **one** test, however, should not be regarded as a wholly dependable index for **all** antibodies.

The sensitized tanned red blood cell hemagglutination test is complex in detail but the principle involved can be explained simply. Agglutination of red blood cells is an easily determined sharp end-point for many immunologic reactions. If the surface of red cells is altered by tannic acid, thyroglobulin antigen can be coated onto the red cells. The addition of serum containing antithyroglobulin antibody to the sensitized tanned cells results in an antigen-antibody reaction manifested by agglutination. The test is highly sensitive. Titers in dilutions of 1/5,000,000 have been observed in our laboratory. The tedious task of preparing standardized reagents has recently been greatly simplified by Fulthorpe. Dependable reagents are now commercially available. The mere presence or absence of antibodies is not diagnostic per se. Both the type and titer of antibody must be considered in the context of the total clinical picture.

Table 4.

METABOLIC DIAGNOSTIC TESTS

B.M.R.	Helpful if low. Usually minus 15% in half the cases.
P.B.I.	Measures any iodinated protein. Usually remains normal but may be decreased or increased.
BUTANOL EXTRACTABLE P.B.I.	Measures only thyroxin and tri-iodothyronine. Low in half of cases. May be low when P.B.I. is normal or high.
SERUM CHOLESTEROL	May be elevated. Rarely of diagnostic help.
SERUM ALPHA-2 AND GAMMA GOLBULIN	Elevated in about ¾ of cases.
FLOCCULATION TESTS	Thymol turbidity and colloidal gold flocculation may be abnormal.
RADIOACTIVE IODINE UPTAKE	Variable, usually normal.
T.S.H. TEST	May be of great help.

Table 5.

THE T.S.H. TEST

PRINCIPLE	1. Determine radioactive iodine uptake. 2. Give T.S.H. 3. Repeat radioactive iodine uptake. 4. Compare uptake results.
UTILIZATION	To distinguish between: Struma lymphomatosa Non-toxic adenomatous goiter Carcinoma of thyroid
INTERPRETATION	Adenomatous goiter and carcinoma usually manifest a 50% increase in RAI uptake. In struma lymphomatosa the thyroid cells are unable to respond to T.S.H., hence there is no significant increase in RAI uptake after T.S.H. because the gland is already under maximal stimulus.

(T.S.H.: Pituitary thyroid stimulating hormone)

Table 6.

TYPES OF THYROID AUTO-ANTIBODIES

ANTI-THYROGLOBULIN ANTIBODY

1. Production evoked by cell free thyroglobulin.
2. Demonstration
   A. Can be demonstrated in serum by:
      a) Hemagglutination tests using coated tanned RBC.
      b) Precipitin tests.
      c) Radioactive coprecipitation.
      d) Passive cutaneous anaphylaxis.
      e) Usually does not fix complement.
   B. Can be demonstrated in thyroid sections
      By Coons' technique on fixed frozen sections with fluorescent anti-thyroglobulin antibody which "stains" antigenic colloid in lumen.

ANTI-MICROSOMAL ANTIBODY

1. Production evoked by microsomal antigen from thyroid epithelial cells.
2. Demonstration
   In serum
   Complement fixation test.
   In tissue
   By Coons' technique on unfixed frozen sections with fluorescent antimicrosomal antibody which "stains" cytoplasmic antigens.

CYTOTOXIC ANTIBODY

Demonstrable in tissue culture studies by the death of growing thyroid cells.

Table 7.

PERCENTAGE OF CASES AND RANGES OF TITER OF CIRCULATING ANTIBODIES IN THYROID DISEASES

	No Antibodies Detected	Weak Titer	Medium Titer	High Titer
Carcinoma of Thyroid	67	23	8	2
Non-Toxic Nodular Goiter	66	21	10	3
Thyrotoxicosis	36	27	35	2
Myxedema	17	16	44	23
Struma Lymphomatosa	3	6	27	64

Percentages approximate. Titers as defined by Doniach and Roitt. Adapted from Doniach and Roitt.

Antibodies also occur in thyroid diseases other than struma lymphomatosa. Table 7 is a conservative estimate, adapted from Doniach and Roitt,[6] of antibody incidence and titer in five common diseases. Blizzard and his co-workers[1] have also provided similar data on thyroglobulin antibodies in multiple thyroid diseases. Aside from the practical problem of differential diagnosis, the implications of this fact are beyond the scope of our present discussion.

The experience of our laboratory with various diagnostic procedures has now been fairly extensive. Our laboratory has used the sensitized red cell agglutination, agar gel precipitation, and agglutination of latex particles sensitized with thyroglobulin technics. In our laboratory at this time the sensitized tanned red cell technic is the most sensitive of the available methods. The sera of patients with struma lymphomatosa may react in titers from 1:250,000 to 1:5,000,000. Not all cases give a positive reaction. About 10% of patients with struma lymphomatosa have no demonstrable antibodies, and about 10% have antibody only to thyroid cell substance ("microsomes"). Precipitin tests are generally regarded as being more specific but less sensitive. The correlation of antibody titers with morphologic findings is a task which still requires further study.

Very high titers of circulating antibodies point strongly to a diagnosis of struma lymphomatosa; titers are usually much lower for carcinoma and nodular goiter. When antibody studies and the diagnostic studies outlined in Table 4 are correlated with the total clinical picture, the accuracy of clinical diagnosis is very high and may be further increased by needle biopsy.

The association of thyroid carcinoma and struma lymphomatosa has received considerable attention. Lindsay, et al.[2] reported the coexistence of malignancy in 12% of one series of cases. Woolner, et al.[11] reported an incidence of 3% of carcinoma, usually low grade papillary carcinoma, in the series of 605 cases reported from the Mayo Clinic. Some surgeons have argued that the risk of associated carcinoma warrants surgical ex-

cision of all cases of struma lymphomatosa. However, most concerned clinicians agree that this incidence figure demands careful assessment of each individual case but definitely does not necessitate "prophylactic" surgical excision for all cases.

Needle biopsy will not always be of help in determining the possible coexistence of carcinoma and struma lymphomatosa because the small tissue sample may not be representative of the entire gland. On the other hand, this technic has been frequently utilized for diagnostic confirmation by clinicians who treat this disease with desiccated thyroid rather than by thyroidectomy. Skillern, et al.[8] have reported 46 instances of needle biopsy at the Cleveland Clinic and McConahey, et al.[4] cite 100 needle biopsies done at the Mayo Clinic. Needle biopsy has been found reliable and satisfactory for the diagnosis of struma lymphomatosa whenever it has been utilized.

Finally, it should be stressed that surgical therapy tends to aggravate thyroid hypofunction whereas therapy with appropriate dosage of desiccated thyroid daily will result in disappearance or marked reduction in the size of the goiter in 90% of cases of struma lymphomatosa.[4,7,8] Several authors have proposed that successful treatment of goiter with thyroid extract is presumptive evidence against adenomatous goiter or adenoma and favors a diagnosis of struma lymphomatosa.[4] Once begun, thyroid extract must be continued for a prolonged period. Patients must be followed to assure the expected satisfactory end result. Surgically treated patients are likely to develop hypothyroidism postoperatively and are in no less need of desiccated thyroid and prolonged follow-up care. Indeed, all of the surgical cases we have been able to follow were placed on desiccated thyroid after the pathologic diagnosis was reported.

SUMMARY AND CONCLUSIONS

Nine recent cases of struma lymphomatosa have been clinicopathologically evaluated.

Struma lymphomatosa is common, not rare; 15% of thyroidectomy specimens were so diagnosed pathologically during 1960-1961. The disease has apparently been increasing in frequency since 1930.

The classic case with a tender, symmetrically diffuse, smooth surfaced mass associated with soreness in the neck was infrequent in our series. As expected, our patients were women between 30 and 50 with a neck mass of variable duration which had recently increased in size or was associated with swallowing difficulty in half the cases. Our cases usually presented with asymmetrical, suggestively nodose masses. With clinical data alone these cases were usually regarded as non-functioning adenomatous goiter, adenomas or possible carcinoma.

The nature, theoretical basis, significance and limitations of available laboratory procedures are discussed. The tests of most help in differential diagnosis are: 1) a low butanol extractable protein bound iodine (B.E.P.B.I.); 2) no significant increase of radioactive iodine uptake after the administration of thyroid stimulating hormone (T.S.H.); 3) a high titer of circulating antibody using the sensitized tanned red blood cell agglutination technic or the precipitin tests; and 4) needle biopsy.

The current status of auto-immune antibodies as etiological factors and as diagnostic indices is reviewed.

Treatment with desiccated thyroid should lead to disappearance or marked regression of the neck mass, correction of manifest hypofunction and alleviation of symptoms in at least 90% of cases.

Carcinoma is said to be associated with approximately 3% of cases. Although this incidence figure warrants careful clinical evaluation of all cases, it does not necessitate surgical therapy for all.

Surgery is no longer regarded as the therapy of choice.

This review is also intended as much to focus attention on further progress to be expected as to summarize recent advances already achieved.

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THE NERVES OF THE CRANIAL DURA MATER AND THEIR SIGNIFICANCE IN DURAL HEADACHE AND REFERRED PAIN*

DONALD L. KIMMEL, Ph.D.**

INTRODUCTION

That nerves are present in the cranial dura mater was known to such outstanding anatomists as Pacchoni, Winslow and Vieussens during the seventeenth and eighteenth centuries. Since this time, the dural nerves have been studied extensively by many investigators. Those who have studied dural nerves include Arnold,[1] Luschka,[2] Dowgjallo,[3] Grzybowski,[4] Hovelacque,[5] Stohr,[6] McNaughton,[7] and Penfield and McNaughton.[8] The descriptions of the nerves in the cranial dura mater given in most textbooks used in anatomy today are based upon the early studies of Arnold and Luschka. These authors were the first to describe the origin and distribution of the nerves in the cranial dura. Arnold described several recurrent branches of the trigeminal nerve to the cranial dura mater and illustrated them in his famous atlas "Icones nervorum capitis."[9] Luschka gave the first accurate account of the nervus meningeus medius. Hovelacque has contributed extensively to our knowledge of the cranial and spinal recurrent meningeal rami.

Recently the nerves in the cranial dura have been re-studied by Penfield and his collaborators. The reports[7,8,10] of this group include accurate accounts of the routes followed by the nerves in the cranial dura mater and the specific origins of the dural nerves derived from the trigeminal nerve. From observations made on neurosurgical patients under local anesthesia, these authors also give excellent accounts of the areas where pain is experienced when nerves in different regions of the cranial dura mater are stimulated. Similar observations on referred pain resulting from stimulating the nerves in the cranial dura mater have been reported by Ray and Wolff.[11]

Until recently, the origins of the nerves supplying the dura mater in the posterior cranial fossa had not been determined with certainty. The dural nerves in the posterior fossa have been described as branches of the hypoglossal,[12] vagal,[1,4,7,13] and glossopharyngeal[6,14] nerves. Rothballer[15] has demonstrated that the second cervical nerve is the source of the nerves in the dura lying anterior to the foramen magnum. Siwe[16] believes that all the nerves to the dura mater in the posterior

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fossa originate from interconnections between upper cervical nerves and the sympathetic trunk. Clinical studies[8,11] on referred pain strongly indicate that the dural nerves in the posterior fossa are branches of the upper cervical nerves. Our own studies, on silver impregnated human fetuses, show very clearly that the nerves in the dura mater lining the posterior cranial fossa are branches of the upper cervical spinal nerves. Our studies also demonstrate that all the dural nerves receive sympathetic contributions, either directly from the sympathetic trunk or from its extensions along cranial blood vessels.

This report is based, in part, upon our studies of the origin, fiber content, and distribution of the nerves in the cranial dura mater in the human fetuses. Since, however, these nerves have not completed their growth in the fetuses, and since we desire to give a complete summary of our present knowledge of the dural nerves, this paper also includes considerable data from the investigators cited above, and especially from the studies of the group at the Montreal Neurological Institute.[7,8,10]

INNERVATION OF THE CRANIAL DURA MATER

The nerve fibers supplying the cranial dura mater are derived from the trigeminal nerve, the upper three cervical nerves, and the sympathetic trunk. Nerve branches from the upper three cervical nerves and the superior cervical ganglion supply the dura mater of the posterior cranial fossa. The dural nerves derived from the three divisions of the trigeminal nerve and from the sympathetic plexuses on the internal carotid and middle meningeal arteries supply the remainder of the cranial dura mater.

NERVES TO THE DURA MATER IN THE ANTERIOR CRANIAL FOSSA

The anterior meningeal nerves supply the dura mater in this area (Figs. 1 and 2). They are branches of the anterior and posterior ethmoidal nerves plus some terminal filaments of the nervus spinosus and nervus meningeus medius. Dural branches of the ethmoidal nerves enter the cranial cavity through the cribriform plate of the ethmoid bone. Their fibers are derived from the ophthalmic division of the trigeminal and from the sympathetic nerve plexus on the internal carotid artery. Branches of these nerves are distributed in the dura mater lining the medial part of the anterior fossa and within the anterior part of the cerebral falx (Figs. 1 and 2). Most of the dural branches lie alongside the anterior meningeal arteries or within the walls of the anterior part of the superior sagittal sinus (Fig. 2).

The nervus spinosus (Figs. 1 and 2) is a recurrent meningeal branch of the mandibular division of the trigeminal nerve. It contains nerve fibers derived from the mandibular nerve and from the sympathetic plexus on the middle meningeal artery. This nerve enters the cranial cavity, with the middle meningeal artery, through the foramen spinosum. Anterior branches of the nerve (Fig. 3) accompany comparable branches of the blood vessel to supply the dura mater covering the orbital and squamosal portions of the frontal bone (Figs. 1 and 2).

The nervus meningeus medius arises from the maxillary division of the trigeminal nerve just proximal to its exit through the foramen rotundum and from the sympathetic plexus on the internal carotid artery (Fig. 1). Anteriorly extending terminal filaments of this nerve supply the dura mater covering the posteriolateral aspect of the anterior cranial fossa.

NERVES TO THE DURA MATER IN THE MIDDLE CRANIAL FOSSA

The nervus spinosus and nervus meningeus medius supply the dura mater in this region (Figs. 1 and 2). The origin of these nerves is discussed above. Branches of the nervus meningeus medius supply the dura mater covering the anterior part of the middle fossa and the dura forming the lateral wall of the cavernous sinus.

The nervus meningeus medius usually consists of two or three separate nerves. These fascicles have been described as originating intracranially from all three divisions of the trigeminal nerve.[8] In all the human fetuses we have studied, tri-

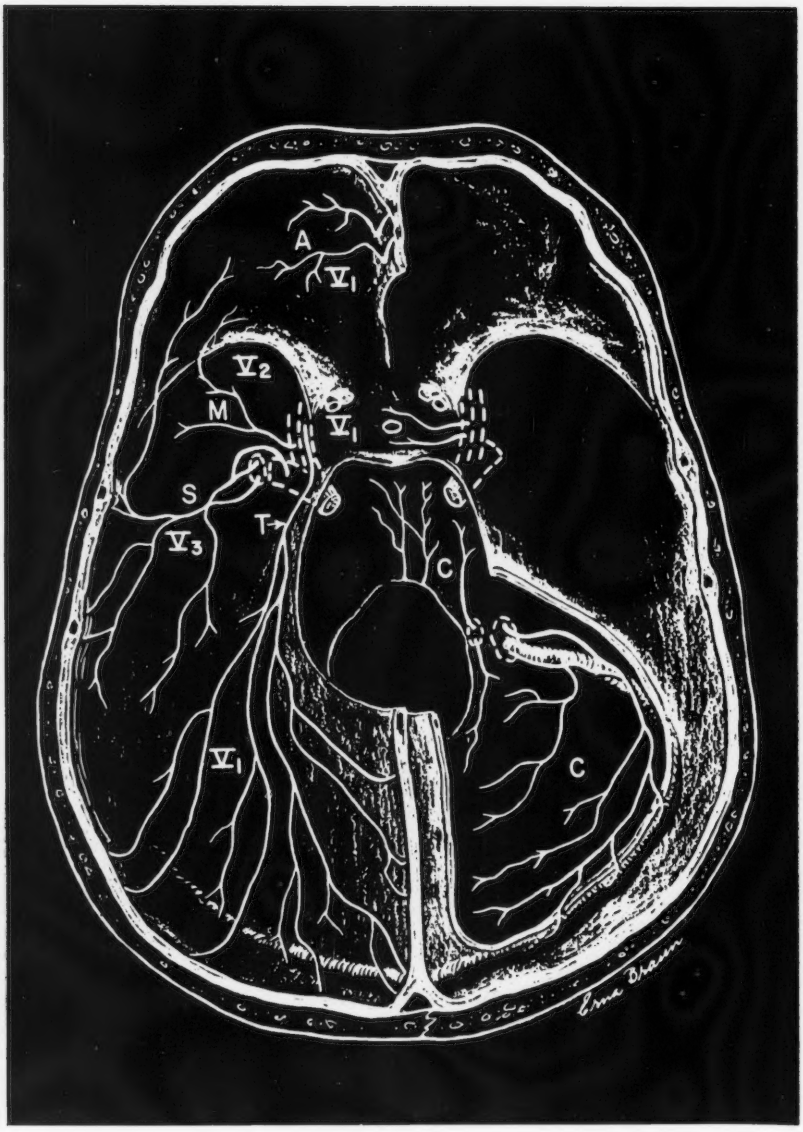

Figure 1.

A diagram showing the origin and distribution of the nerves in the dura mater lining the three cranial fossae and in the tentorium cerebelli. The tentorium has been removed on the right. The anterior meningeal nerve (A), nervus meningeus medius (M), nervus spinosus (S), and the tentorial nerve (T) are illustrated on the left side only; the dural nerves in the diaphragma and the nerves of cervical origin (C) in the dura mater of the posterior cranial fossa are shown only on the right side of the figure. V_1, V_2 and V_3 designate branches of the ophthalmic, maxillary, and mandibular divisions, respectively, of the trigeminal nerve. Compare with Figure 2.

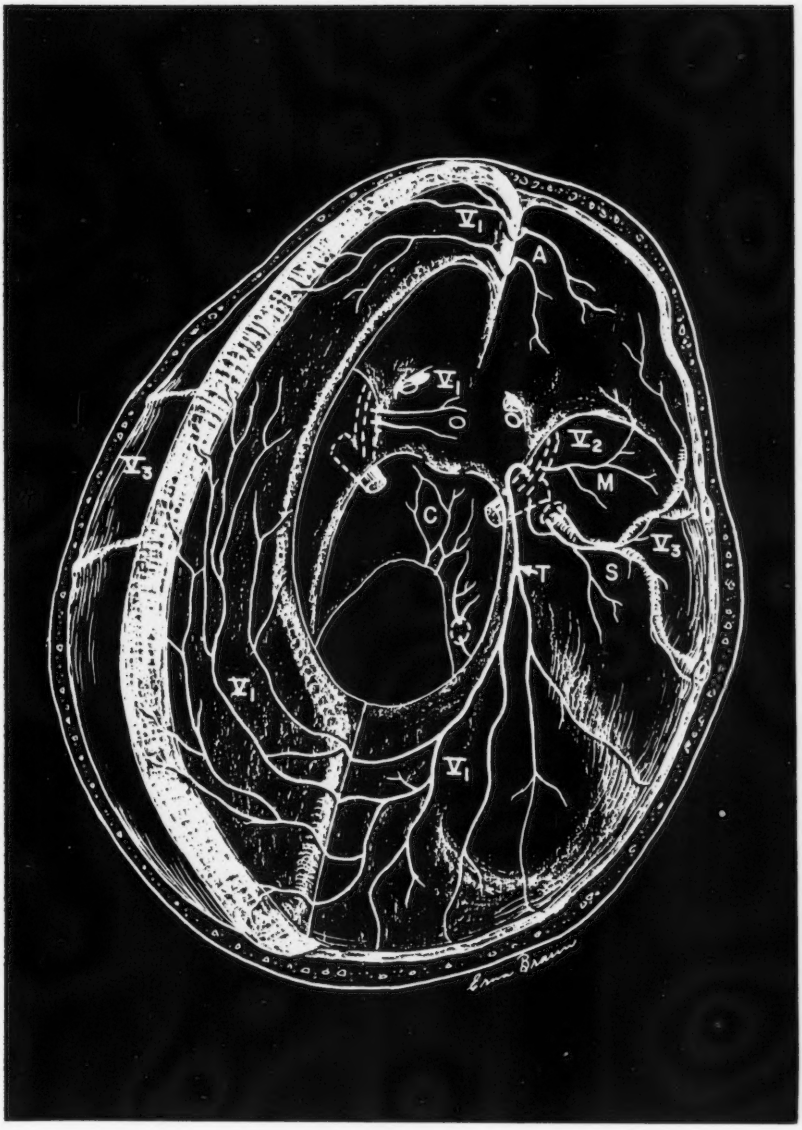

Figure 2.

The nerves in the cranial dura mater viewed from above and behind. Labels are the same as in Figure 1. Note the extensive distribution of the tentorial nerve (T) in the tentorium cerebelli and in the cerebral falx. Note also the branches of the nervus spinosus, labeled V_3 on the left, which extend into the superior sagittal sinus. Compare with Figure 1.

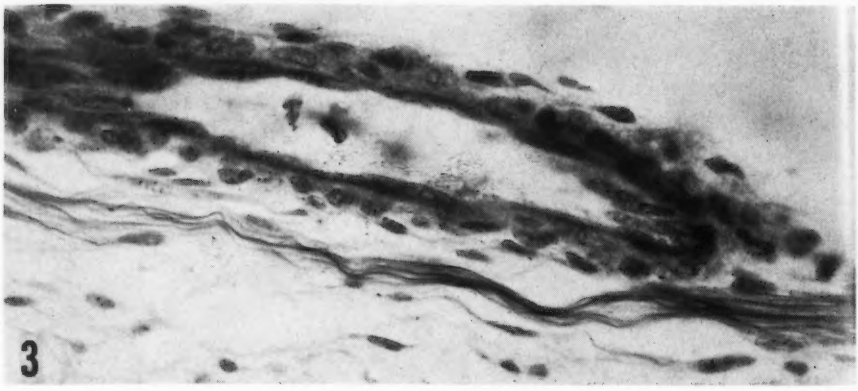

Figure 3.
Photomicrograph from a 33 mm human fetus of the anterior branch of the middle meningeal artery and its nerve plexus. The nerve plexus, below the artery, is from the nervus spinosus and contains sensory (pain) fibers from the mandibular nerve and vasoconstrictor fibers from the middle meningeal sympathetic plexus. Holmes' silver; X 280.

geminal contributions to the nervus meningeus medius originate only from the maxillary division of the trigeminal. Other nerve fascicles present in this area (Fig. 1), which may appear to originate from the first and third divisions of the trigeminal or directly from the semilunar ganglion in adult material, are sympathetic nerve filaments. They are closely adherent to the trigeminal ganglion and its branches as they course around these structures to join both the nervus meningeus medius and the nervus spinosus.

Branches of the nervus spinosus are distributed to the dura mater in the posterior and lateral parts of the middle cranial fossa. Most of these branches are closely related to the middle meningeal artery. Branches of the nervus spinosus continue beyond the middle fossa. They follow the anterior (Fig. 3) and posterior branches of the middle meningeal artery superiorly to supply the dura mater lining most of the calvaria. At the region of the vertex of the skull, branches of the nervus spinosus extend into the walls of the superior sagittal sinus and into the intermediate portion of the cerebral falx (Figs. 2 and 3).

NERVES TO THE DURA MATER OF THE HYPOPHYSEAL FOSSA AND DIAPHRAGMA SELLAE

The nerves in the dura mater in this area are composed of fibers from the ophthalmic division of the trigeminal nerve and from the sympathetic plexus on the internal carotid artery. The ophthalmic contribution may arise directly from the ophthalmic trunk or from either its frontal or tentorial branch. These nerves accompany the inferior hypophyseal arteries for a short distance and then become associated with the intercavernous venous sinuses. Usually an anterior and a posterior dural nerve enter the diaphragma on each side of the midline (Figs. 1 and 2). One or two nerve filaments supply the dura mater lining the hypophyseal fossa.

NERVES TO THE TENTORIUM CEREBELLI AND THE POSTERIOR PART OF THE CEREBRAL FALX

These folds of dura are supplied by the tentorial nerve (Figs. 1, 2 and 4). This nerve was first described by Arnold,[1] who believed it to be a branch of the trochlear nerve. In the fetuses, the tentorial nerve arises in the posterior part of the orbit from the frontal branch of the ophthalmic division of the trigeminal nerve. It receives one or two fairly large fascicles from the sympathetic plexus on the internal carotid artery and, following a recurrent course, enters the cranial cavity through the superior orbital fissure. In the proximal part of its course within the cranial cavity, the tentorial

nerve lies in the dorsolateral wall of the cavernous sinus close alongside the trochlear nerve and the tentorial artery (Fig. 4).

Near the posterior clinoid process, the trochlear nerve separates from the tentorial nerve and artery to enter the subarachnoid space, while the tentorial nerve and artery divide into several branches and continue posteriorly within the tentorium and the posterior half of the cerebral falx. Terminal branches of the tentorial nerve are distributed to the tentorium cerebelli, the posterior half of the cerebral falx, the walls of the straight sinus, the caudal parts of the superior and inferior sagittal sinuses, the upper wall of the transverse sinus, the cerebral veins entering these sinuses, and the dura mater lining that part of the calvaria which surrounds the occipital lobe of the cerebrum. Most of the branches of the tentorial nerve terminate in the walls of the venous sinuses and cerebral veins, or along the branches of the tentorial artery. Only a few nerve filaments end in the cerebral falx and tentorium independent of their vascular structures.

NERVES TO THE DURA MATER IN THE POSTERIOR CRANIAL FOSSA

The nerves supplying the dura mater lining the posterior cranial fossa are derived from the upper three cervical nerves and from the superior cervical ganglion.[17] They enter the cranial cavity through the foramen magnum, the jugular foramen, and the hypoglossal canal.

The dural nerves entering the cranial cavity through the foramen magnum (Fig. 5) are rostrally coursing, terminal branches of the 2nd and 3rd cervical nerves. They enter the cranial dura mater at the ventral border of the foramen magnum and supply the dura mater covering the clivus and dorsum sellae.

The meningeal nerves entering the posterior cranial fossa through the hypo-

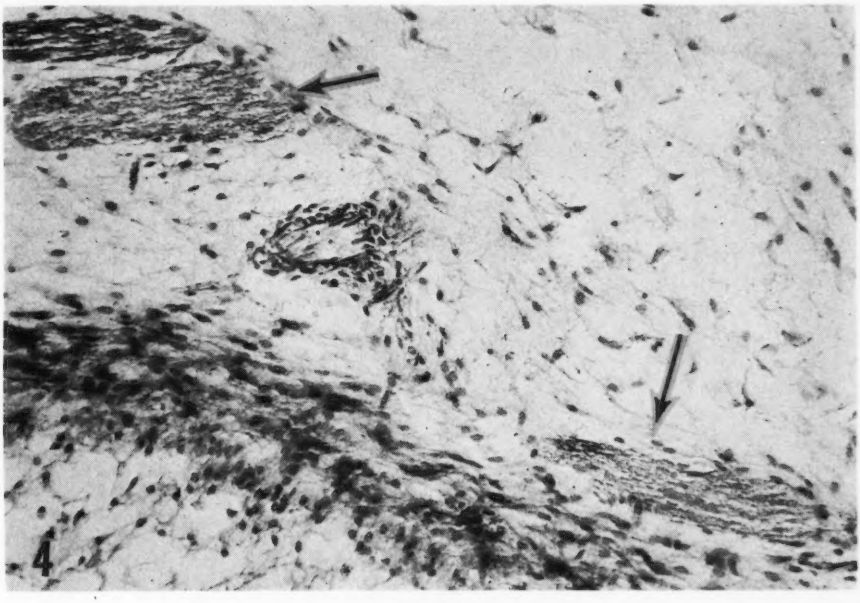

Figure 4.
Photomicrograph from a 46 mm human fetus showing the tentorial nerve (two branches indicated by arrows) with the tentorial artery (center of figure) and the trochlear nerve (upper left). These three structures run together in the dorsolateral wall of the cavernous sinus. Note the lighter silver impregnation and small nerve fibers in the fasicles of the tentorial nerve compared to the darker impregnation of the larger, somatic efferent fibers in the trochlear nerve. Holmes' silver; X 150.

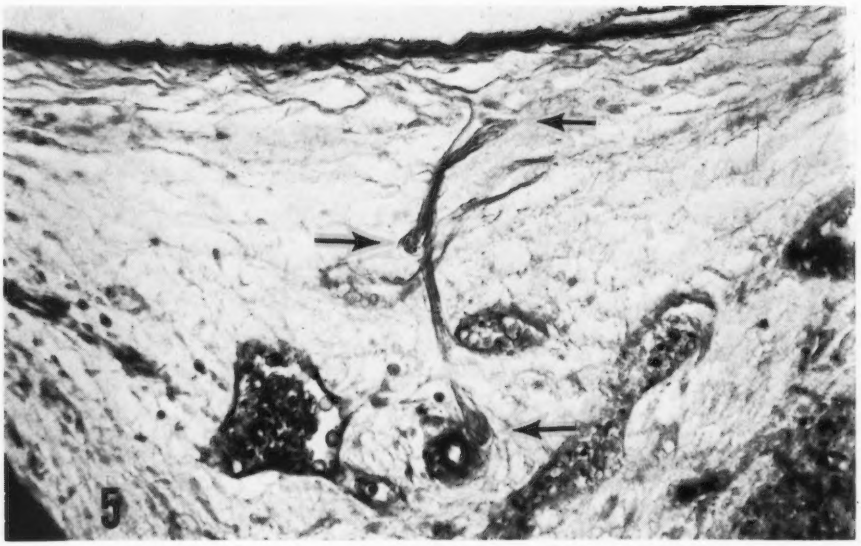

Figure 5.
Photomicrograph from a 47 mm human fetus taken at the ventral margin of the foramen magnum. The lower two arrows indicate two ascending nerves whose fibers are derived from the recurrent meningeal nerves of the upper three cervical spinal nerves—but mostly from the second cervical nerve. Note the branches from these nerves extending into the meningeal layer of the dura mater (upper arrow). These dural nerve fascicles supply the dura mater covering the clivus and dorsum sellae. Holmes' silver; X 260.

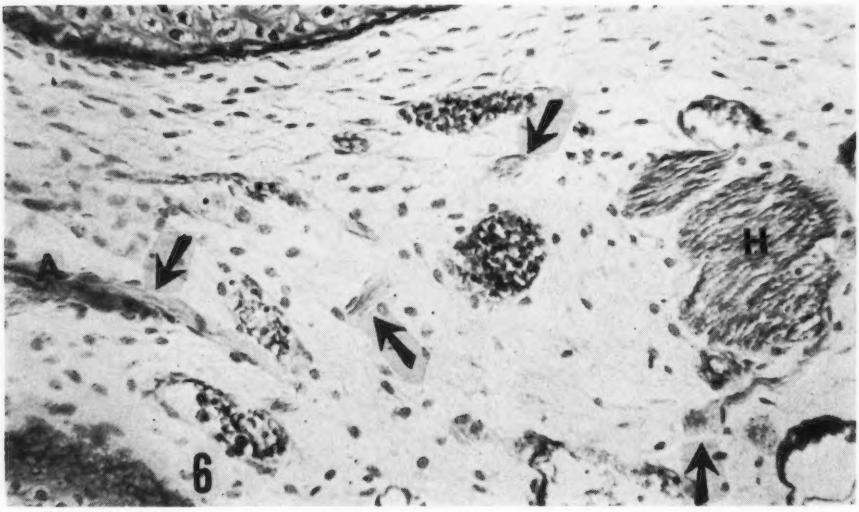

Figure 6.
Photomicrograph from a 33 mm human fetus taken through the hypoglossal canal. This figure shows the dural nerves of cervical origin (arrows) which accompany the hypoglossal nerve (H) and the meningeal branch of the ascending pharyngeal artery (A) into the posterior cranial fossa. Holmes' silver; X 280.

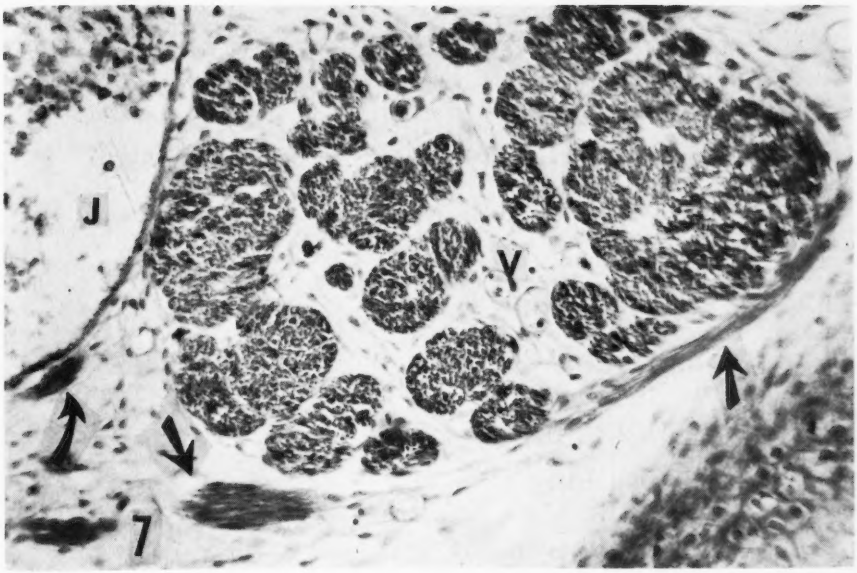

Figure 7.
Photomicrograph taken at the region of the jugular foramen of a 47 mm human fetus showing the dural nerves of cervical origin (arrow) which follow the vagal nerve (V) into the posterior cranial fossa. Note that the dural nerve branches are composed of smaller nerve fibers and are less heavily impregnated than those of the vagus. Note also the dural nerve fascicles leaving the periphery of the vagus to climb upon the wall of the jugular bulb (J). Holmes' silver, X 280.

glossal canal (Fig. 6) and the jugular foramen (Fig. 7) derive their nerve fibers from muscular branches of the 1st and 2nd cervical nerves and from the superior cervical ganglion. These dural nerve branches follow and are closely adherent to the glossopharyngeal, vagal, and hypoglossal nerves, and the meningeal branch of the ascending pharyngeal artery as the dural nerves course rostrally into the cranial cavity (Figs. 6 and 7).

Usually two small dural nerves of cervical origin enter the cranial cavity through the hypoglossal canal (Fig. 6). They supply the dura mater covering the lateral margin of the foramen magnum and the adjacent medial part of the posterior cranial fossa (Figs. 1 and 2).

Two to four dural nerves of cervical origin enter the cranial cavity via the jugular foramen (Fig. 7). As they enter the skull, these nerves attach themselves to the walls of the sigmoid sinus. They follow the sigmoid sinus laterally and then turn posteriorly on the inferior wall of the transverse sinus. Their terminal branches supply the sigmoid sinus, the inferior wall of the transverse sinus, the occipital sinus, the cerebellar falx, and the dura mater in the lateral and posterior parts of the posterior cranial fossa (Fig. 1).

DURAL NERVES AND HEAD PAIN

The mechanisms responsible for producing head pain are not well understood. Ray and Wolff[11] have studied the probable causes of headaches extensively and, from observations made on many patients during surgical procedures on the head, they concluded that the pains result primarily from inflammation, traction, displacement, and distention of cranial vascular structures. The studies of Ray and Wolff,[11] Penfield and McNaughton,[8] Feindel, Penfield and McNaughton,[10] Northfield,[18] and many others have demonstrated conclusively that stimulation of the nerves in the cranial

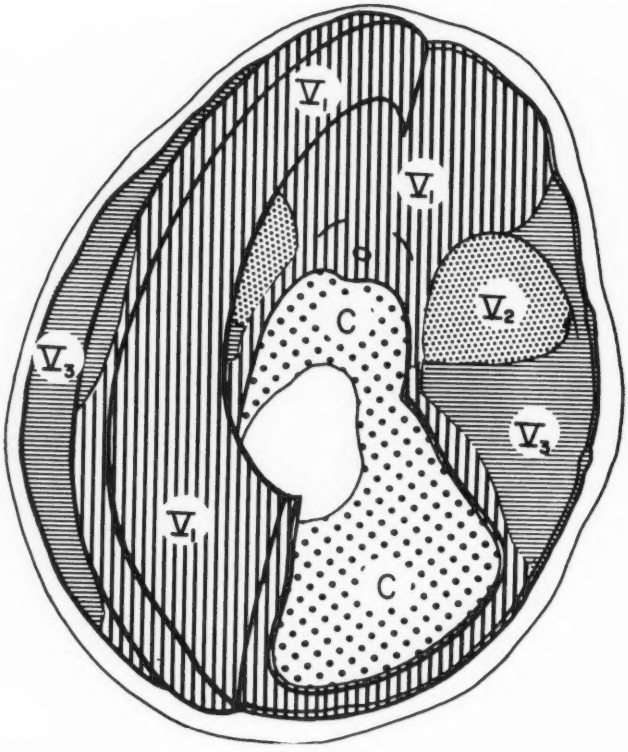

Figure 8.

The cranial dura mater viewed from above and behind. The tentorium cerebelli has been cut away on the right side. Parts of the cranial dura mater which are supplied by each of the three divisions of the trigeminal nerve and by the upper three cervical spinal nerves are indicated. Compare with Figure 9.

dura mater produces pain. This pain may be localized at the area stimulated or it may be referred to the dermatome of the nerve involved. The investigators cited above also have demonstrated that all cranial dura mater is not equally sensitive. The most sensitive areas of the cranial dura mater are those portions forming the walls of the venous sinuses, the dura surrounding the meningeal arteries, and that lining the cranial fossae. Terminal portions of the cerebral veins, which are innervated by the same nerves as the venous sinuses into which these veins drain, are also very pain-sensitive. Non-vascular parts of the dura mater are relatively or completely insensitive.[9,11]

The portions of the dura mater innervated by each of the three divisions of the trigeminal nerve and by the upper cervical nerves are outlined in Figure 8. The dermatomes of these nerves on the face, head, and neck are shown in Figure 9. Irritation of a nerve in the dura mater produces pain. This pain may be localized in the area of the dura stimulated, or the pain may be referred to the skin area (dermatome) supplied by branches of the same nerve that gives origin to the dural nerve branch. Knowledge of the branching patterns of the nerves which contribute branches both to the cranial dura and to the skin is extremely important in determining sites of intracranial pathology (Figs. 8 and 9).

On the basis of the anatomy of the nerves supplying the cranial dura mater, one may be able to predict with consid-

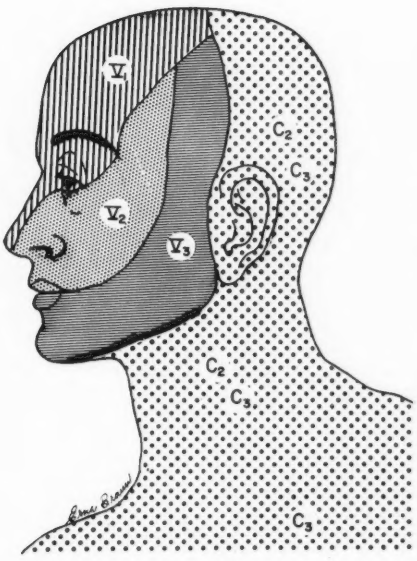

Figure 9.

Outlines of the dermatomes of each of the three divisions of the trigeminal nerve and of the second and third cervical nerves. These nerves supply cutaneous branches to the skin areas designated in this figure and also dural nerve branches to the parts of the dura mater indicated in Figure 7 by the same designs. Pain of dural origin is referred to the dermatome of the nerve involved in the intracranial pathology.

erable accuracy the location of intracranial lesions. Generally speaking, lesions involving the dura mater above the tentorium (the dura mater supplied by the trigeminal nerve) produce pain in face, eyes, and frontal part of the head (Figs. 8 and 9). Pathology in the cranial dura beneath the tentorium (the dura mater supplied by the upper cervical nerves) produces pain in the occipital and mastoid regions, about the external ear, and in the neck (Figs. 8 and 9). However, we can be more specific than this because we know the exact distribution of each of the three divisions of the trigeminal nerve to both the cranial dura mater and to structures outside the cranial cavity (Figs. 8 and 9).

The first division of the trigeminal nerve supplies the dura mater in the anterior cranial fossa, the diaphragma sellae, nearly all the cerebral falx, the tentorium cerebelli, the superior sagittal sinus, the inferior sagittal sinus, the straight sinus, the superior wall of the transverse sinus, and the terminal parts of the cerebral veins entering these sinuses (Fig. 3). Stimulation of the nerves in these regions of the dura mater, whether it be by artificial means during brain surgery or as the result of pathology, produces pain in the frontal region. The pain is experienced in the scalp, forehead, and orbital area. These are the regions of distribution of the extracranial branches of the *ophthalmic* division of the trigeminal nerve (Fig. 9).

Branches of the *maxillary* division of the trigeminal nerve supply the dura mater in the anterior part of the middle cranial fossa (Fig. 8). Stimulation of these dural nerves of maxillary origin produces pain which is referred to the region of the upper jaw and cheek. These areas of the face are supplied by the extracranial branches of the maxillary nerve (Fig. 9). Branches of the third, or *mandibular*, division of the trigeminal nerve supply the dura mater in the posterior and lateral parts of the middle cranial fossa and most of the dura mater lining the calvaria (Fig. 8). Stimulation of these dural nerve branches results in pain which is referred to the mandibular, temporal, zygomatic, and parietal regions of the face and head (Fig. 9).

The dural nerve branches derived from the right and left *ophthalmic* nerves apparently do not overlap one another in their distribution in the walls of the superior sagittal sinus. Stimuli applied to the right wall of this sinus, or to the terminations of the right cerebral veins emptying into it, produce pain in the right frontal region. Stimulating the left wall of the sinus produces pain on the left frontal area. Similarly, stimulation of the ophthalmic nerve branches in the superior wall of the transverse sinus results in pain in the frontal region, while stimulation of the dural nerve branches of cervical origin in the inferior wall of the transverse sinus produces pain in the occipital and cervical regions (Fig. 9).

Pain also is referred to the occipital and upper cervical regions when the nerves in the dura mater of the sigmoid

sinus and on the clivus, dorsum sellae, and margin of the foramen magnum are stimulated. The pain is referred to the occipital and upper cervical areas along cutaneous nerves supplying these areas; these cutaneous nerves are branches of the same cervical nerves that give origin to the nerves in the dura mater in the posterior cranical fossa.

Since pain of posterior cranial fossa origin is usually referred to the upper cervical and occipital regions,[8,11] which are areas supplied by the 2nd cervical nerve, the 2nd cervical segment must supply most of the nerve fibers to the dura mater in the posterior fossa. This we found to be the case in our studies of the human fetuses.

CONCLUSIONS

1. The cranial dura mater is innervated by branches of the three divisions of the trigeminal and by the upper three cervical spinal nerves.

2. The trigeminal nerve supplies all the cranial dura mater except that lining the posterior cranial fossa. Each division of the trigeminal nerve supplies a specific part of the supratentorial dura mater.

3. The dura mater of the posterior cranial fossa is innervated by branches of the upper three cervical spinal nerves. The second cervical nerve supplies most of the nerve fibers distributed to this region.

4. Most of the nerves in the cranial dura mater are distributed to blood vascular structures, i.e., to the meningeal (dural) arteries, the venous sinuses, and the terminal parts of the cerebral veins.

5. Stimulation of the dural nerves produces headaches. The pain may be experienced locally or referred to parts of the face, head, and upper cervical region. The referral of pain to specific areas of the head, face, and neck, when nerves in a particular part of the dura mater are stimulated, is discussed.

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CLINICAL PATHOLOGICAL CONFERENCE

Myxedema, Diabetes Mellitus, Heart Failure, Nephrosis, Hypothermia, Coma

CLINICAL ABSTRACT

1st Admission:

The patient was first admitted to Mount Sinai Hospital on September 22, 1946, at the age of 22, with complaints of backache and severe thirst present for one day. Polyuria, polydipsia, weakness, anorexia and weight loss had been present for the previous six months. For a few days prior to admission, vomiting had been noted after meals.

Past illness included whooping cough, measles, and mumps. She was a twin; her twin sibling died at birth. Her mother stated that her early development had been normal, noting that she walked at eleven months and talked at an early age. She was the only short member of her family; the remaining members of the family were of normal stature. Her mother said she started getting "sluggish" at the age of eight at which time desiccated thyroid therapy was begun but no details of diagnostic studies at that time are available.

Physical examination revealed a dehydrated white female with Kussmaul respirations. Blood pressure was 100/60 and pulse 100. A small red pin point area was described above the left optic disc. The eyeballs were soft. A systolic murmur was heard in the aortic area. The remainder of the examination was negative.

After appropriate studies the patient was treated for diabetic ketoacidosis and made a rapid recovery, following which she was maintained on insulin therapy.

During this hospitalization the basal metabolic rate was low on two occasions.

At the time of her discharge she was placed on 120 mgm. of desicated thyroid and 20-25 units of globin insulin daily.

Clinical Discussion:
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Emanuel E. Mandel, M.D.***

Radiology:
Jerome Nadelhaft, M.D.****

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2nd Admission:

The patient did well and worked regularly, rarely missing a single work day until September, 1960, when she entered the hospital because of the sudden onset of severe dyspnea, nausea and vomiting which was followed by a cramping epigastric pain which radiated to both shoulders. She was given "shots" and oxygen at home which resulted in improved breathing but vomiting persisted. Swelling of the abdomen had been noted for the previous two weeks and swelling of the feet and ankles for two days prior to admission. Hypertension was observed in 1959 following which she received daily chlorthiazide.

Her last menstrual period was in August of 1960; her previous periods being at approximately three month intervals with profuse bleeding. Intake of thyroid hormone had been discontinued shortly before this admission but the exact period of time between discontinuance of thyroid medication and onset of symptoms was not known.

Physical examination revealed a B.P. of 222/108 and a pulse of 120. Height was 57 inches and her weight was 87 lbs. She was pale, with thick and dry skin, coarse hair and puffy eyes and lips. Funduscopic examination revealed grade iii Keith Wagner hypertensive retinopathy and changes characteristic of diabetes mellitus. There was cardiomegaly to the left anterior axillary line, and an apical systolic murmur was heard. There were crepitant rales throughout both lung fields and dullness in both bases. The abdomen was distended, a fluid wave and shifting dullness being readily elicited. The liver edge was palpable three fingerbreadths below the right costal margin. 2+ pitting edema of the lower extremities was noted.

Digitalis, mercurial diuretics and aminophyllin were administered with gradual improvement of signs and symptoms during the next four days.

Her admission blood sugar was 1016 mgm.% and following the administration of 70 units of crystalline insulin during the following ten hours, the blood sugar fell to 120 mgm.% and then to clinically hypoglycemic levels which responded rapidly to intravenous glucose.

Diuretic and insulin therapy were continued throughout the hospitalization and following the return of thyroid function tests, desicated thyroid was started. Four days later it was discontinued because of a rapid rise in her blood sugar. She was discharged after 18 days of hospitalization on protamine zinc insulin and chlorthiazide.

3rd Admission:

Six weeks later, in November, 1960, she was readmitted because of severe low back pain, of one week duration, radiating to both feet. The pain had its onset while the patient was having a bowel movement and it increased in severity during the week prior to admission. Paresthesia of both feet was present during this same period. There were no cardiorespiratory complaints. Weakness and fatigue were present.

Physical examination revealed a B.P. of 190/130 and pulse of 80; weight was 90 lbs. The remainder of the physical examination was essentially similar to the previous admission except for the absence of pulmonary signs and the presence of tenderness over the lower lumbar vertebrae and sacroiliac joints. Deep tendon reflexes were decreased. She was placed on rauwolfia derivatives, PZI insulin and codeine for pain.

Her back pain improved and the diabetes was easily controlled until one week after admission when she noted episodes of feeling cold and dizzy together with severe diaphoresis. These symptoms responded to intravenous glucose. During one of the attacks when the patient lost consciousness the blood sugar was 30 mgm.%. Long acting insulin was discontinued and only crystalline insulin was administered thereafter. At this time, distension and tympany of the abdomen developed. Bowel sounds were normal and there was no abdominal tenderness. Rectal examination was negative and enemas did not relieve the distension.

The patient gradually became more lethargic and finally semicomatose. The rectal temperature was noted to be 93.1°F.

On 12/6/60 oral triiodothyronine, hydrocortisone and a warming blanket

	First Admission	Second Admission				Third Admission						
	8-22-46	9-28-60	9-29	10-9	10-15	11-22	11-26	11-28	12-1	12-4	12-5	12-8
Hemogram												
Hemoglobin	16.2	8.1			10.7	10.7			11.9			7.4
RBC	4.96	3.23			3.66	4.05			4.5			
Hematocrit		26			34	34			37			27
WBC	10000	21500			11100	10950			10150			
polys	69	72			78	67			67			
stabs	4	19			4	6			20			
eos		1			1	1			1			
lymphs	24	4			13	20			13			
monos	3	4			4	6			2			
Total Eos/mm^3									44			
Blood												
Glucose	385	1016	120	936	78	139	152	30	32	262	30	940
BUN		32			70	42		31		19		32
Creatinine		1.8			1.7			1.8				3.4
Cholesterol -- total								420				
% esters								73				
Total protein		5.2						6.5				
A/G ratio		2.2/3.0						3.0/3.5				
Sodium		133					110		116			112
Potassium		4.7					4.6		3.6			3.6
Chloride							79		77			69
CO_2 combining power		26							26			12
Serum pH									7.4			
Serum acetone										neg		neg
Urine												
Specific gravity	1.010	1.018										
Protein	1+											
Glucose	0.75											
Acetone										neg		neg
Quant. sugar (gms/24 hr)		15							3.0			
Quant. protein "		6.45										
Sediment												
WBC	occ											
RBC		3-5										
Casts		neg										

MISCELLANEOUS LABORATORY REPORTS

BMR	1946	Minus 19%	Minus 26%
PBI	10/ 5/60	2.8 Gamma %	
	11/23/60	1.5 Gamma %	
24 hour I^{131} uptake	12/ 3/60	2.3%	
T_3 Uptake	12/ 3/60	12%	

Microscopic examination of urine for oval fat bodies

11/29/60 Negative

I^{131} BSA Blood Volume Studies

12/ 3/60	Cell Mass	Plasma Volume	Blood Volume
Determined	888	2072	2960
Expected	1230	1763	2993
Deficit	—342	+309	—33

ECG 9/28/60 Left ventricular hypertrophy. Minor lateral wall ischemic changes.

were added to the regimen. The following day oral triiodothyronine was replaced by intravenous triiodothyronine* and she showed marked improvement, becoming more alert and responsive to questioning. 250 mcg. of intravenous triiodothyronine was given during the 24 hour period. Body temperature had risen to 98°F. rectally. The abdomen remained distended and the nasogastric tube began to drain coffee-colored, hematest + material.

On 12/8/60 she appeared more alert. Triiodothyronine dosage was reduced on 12/9 to 75 mcg. per day.

On 12/9/60 she was found to be confused and in shock with a blood pressure of 90/40. The reason for this sudden marked worsening was not apparent. Laboratory data at this time revealed a hemoglobin of 7.2 gm.%; CO_2 of 12 mEq/L; blood sugar of 940 mgm.% and negative urine and serum acetone. 1 unit of packed cells was given and the B.P. increased to 150/90. A few hours later the patient expired.

* Kindly supplied by Smith Kline and French Laboratories.

RADIOGRAPHIC FINDINGS

Dr. Jerome Nadelhaft:

We have no films from the first admission in 1946.

A bedside chest film made at the second admission in September, 1960, showed a calcified primary complex in the right hemithorax. The middle mediastinal image was suggestively enlarged in a nonspecific fashion. At least part of its large appearance was attributed to the bedside technique. There was evidence of pulmonary congestion in the peripheral vessels in the superior half of each lung although the central pulmonary vessels were not enlarged. There was also some pulmonary edema. The clarity of the lung bases was attributed to vasospasm. The size of the middle mediastinal image (heart) on this film does not correlate well with the clinical finding of cardiac enlargement to the anterior axillary line.

Lumbosacral spine films were made when she was admitted with back pain in November, 1960. These films showed generalized demineralization and overprominence of the margins of the vertebral bodies characteristic of osteoporosis. There was no evidence of a partial

collapse of any vertebral body or any other specific abnormality to account for the back pain. There was a small plaque of calcification in the abdominal aorta, a typical finding in a relatively young individual with long standing diabetes.

The skull films revealed a normal sella and no other significant abnormality. On 12/2/60, three-position films of the abdomen showed remarkable gastric dilatation but no other significant abnormality. These findings are typical of acute gastric dilatation.

On 12/9/60, the day of the patient's demise, a bedside chest film demonstrated pulmonary edema. Again the middle mediastinal image (heart) appeared somewhat enlarged. In addition, there was evidence of subcutaneous edema of the soft tissues of the chest and abdomen, a finding consistent with anasarca.

DISCUSSION

Dr. Leigh Rosenblum:

In essence we have a patient who had the clinical diagnosis of hypothyroidism for 29 years, diabetes mellitus for 15 years, hypertension for 2 years, heart and renal disease during her last year of life, and whose terminal event seems to have been an uncommon complication of a common disease.

We shall direct our attention to sorting out the multiple individual facets of this complicated clinical problem.

Until the age of 8 years, her growth and development was supposedly normal, but at this time hypothyroidism was suspected and from that time until just prior to her terminal illness she was treated with desiccated thyroid. Clinical features and laboratory studies performed during her adult life supported the diagnosis of hypothyroidism. Significant laboratory data include the low BMR's at the age of 22 and the low 24 hour I^{131} uptake by the thyroid gland. The low serum protein bound iodine and high serum cholesterol may have resulted from either of two disease entities in this patient: hypothyroidism and the nephrotic syndrome, as will be discussed later.

The normal red blood cell Triiodothyronine I^{131} uptake (T_3 uptake) could be the resultant of two opposing factors: hypothyroidism reduces the T_3 uptake while the nephrotic syndrome tends to elevate the T_3 uptake. In the presence of both diseases we might expect a normal result.

Etiology of Hypothyroidism

Since the patient had hypothyroidism, the etiology of the thyroid deficiency must be considered. Was it primary thyroid gland deficiency or secondary failure due to anterior pituitary or hypothalamic disease? I was impressed with the marked sensitivity the patient demonstrated to exogenous insulin, the relatively prolonged periods of hypoglycemia, the lack of ketone body formation and the patient's short stature. These phenomena can all be explained by the lack of glucocorticoid and/or growth hormone and it is tempting to suggest the thyroid deficiency was accompanied by absent or deficient adrenocorticotropic (ACTH) hormone and/or growth hormone and was therefore due to pituitary disease.

However, we can probably relate all the above mentioned abnormalities to primary thyroid failure. First, the short stature may be due to thyroid hormone deficiency since the optimal effect of growth hormone requires the presence of thyroxin (T_4) or triiodothyronine (T_3) and in a recent study it was shown that the absence of thyroid hormone inhibits growth hormone release from the pituitary gland.

Second, hypoglycemia is said to be a rare complication of primary myxedema. Catecholamines cause glycogenolysis and increase free fatty acid mobilization from fat depots. The presence of thyroid hormone is an important factor in the tissue response to epinephrine and norepinephrine and we might postulate that in the absence of T_3 and T_4 the catecholamine action is inhibited and hypoglycemic unresponsiveness results, along with decreased free fatty acid mobilization to the liver and subsequent ketone body formation. However, it must be emphasized that most patients with decreased thyroid function appear to respond normally to hypoglycemia.

Further evidence against anterior pituitary or hypothalamic disease is provided by the report of menstrual periods until shortly before the second admission and the normal 17-OH corticosteroids in the urine, which implies normal gonadotrophin and ACTH secretions, respectively. A selective thyrotrophin (TSH) deficiency cannot be excluded by the available data, but since this is so unusual I believe the patient had primary hypothyroidism. Selective TSH deficiency could only have been proved by demonstrating increased thyroid function following the administration of thyrotrophic hormone.

Patients with primary myxedema may be divided into 2 groups: those with and those without goiters. Since this patient had no history of a goiter and the thyroid was not palpated, iodine deficiency and enzymatic defects, either familial or drug induced, may be eliminated as a cause of the hypothyroidism. In patients without goiter and in whom radioactive iodine was not administered and the thyroid was not surgically removed, idiopathic atrophy of the thyroid is the most likely cause of the hormone deficiency. Since the patient's early development was normal, she probably was not athyrotic at birth. Some investigators believe that thyroid atrophy is an auto-immune phenomenon similar to Hashimoto's disease.

Related Symptoms

Before leaving the discussion of the thyroid, two other features of the patient's illness which might relate to thyroid hormone deficiency should be mentioned: her neurologic and gastrointestinal complaints.

Her main symptoms at the time of her last admission were back ache and paresthesias. Quite properly it was thought that the patient had neuritis secondary to diabetes mellitus. However, neurologic disease is commonly associated with hypothyroidism. Neurologic and psychiatric complaints include paresthesia, headaches, sensory loss, dysarthria, depression, and psychosis, and may simulate a brain tumor. Abnormal laboratory studies include an increase in cerebrospinal fluid protein and pressure and an abnormal EEG. Neurologic and psychic symptoms disappear on thyroid therapy if hypothyroidism is the cause of the disturbance.

During the terminal illness severe abdominal distension occurred which was thought to be due to ascites and distension of the G. I. tract. Ascites is rarely associated with myxedema and in this patient was probably due to the nephrotic syndrome. Distension of the colon and stomach has been noted in myxedema and may be due to myxedematous infiltration of the intestinal wall and/or electrolyte disturbances. In this patient, the severe distension of the stomach wall may have resulted in the terminal G. I. bleeding.

The Diabetic Process

The second major disease entity, diabetes mellitus, became apparent 14 years after the clinical appearance of hypothyroidism. We are all aware of the common clinical experience that both insulin requirements and the tendency for ketosis and acidosis increase in patients with diabetes mellitus in whom thyrotoxicosis develops. Also, diabetes mellitus may first become apparent with the appearance of thyrotoxicosis or following the administration of thyroid hormone. Conversely, when the supply of thyroid hormone decreases in patients with diabetes mellitus, the insulin requirement is likely to diminish, especially in the older obese insulin-insensitive patients. Diabetes mellitus has been said to develop less frequently in hypothyroid patients, but this has been questioned recently and further studies will be necessary to record the incidence of diabetes mellitus in hypothyroid patients.

From the data available in the protocol during the 14 years from 1946 to 1960, there was remarkably little variation in her diabetic control considering that she had "juvenile" type diabetes. There was no history of hypoglycemia or ketosis and her insulin requirement remained relatively constant between 15 and 25 units daily. It must be admitted, however, that we do not know the strictness of the diabetic control duuring this entire period.

The patient demonstrated the frequent complications of diabetes: retinopathy, nephropathy and probably neuropathy. The renal and cardiac lesions will be discussed later by Drs. Mandel and Bernstein, respectively. During the patient's last two hospitalizations, the striking fluctuations from hyper- to hypoglycemia with minimal amounts of insulin deserve comment. The basis of this marked insulin sensitivity is not clear, although we may postulate that plasma insulin antagonists normally present were absent or diminished in quantity. Once a patient has demonstrated marked insulin sensitivity, it must be emphasized that all future insulin must be given with caution and in minimal amounts to avoid the serious consequences of hypoglycemia.

Dr. Arthur Bernstein:

I first saw this patient on the morning of her second hospital admission on September 28, 1960, when she came in with acute left heart failure and pulmonary edema. Her hypertension had been known for the past few years. She also had edema for the past several months which had been treated with chlorthiazide but she had not been previously digitalized. She came in via ambulance and was immediately treated with morphine, mercurials, digitalis and oxygen.

On admission she was very pale. The pallor of myxedema is due, of course, to the edema of the skin. In this case, however, there was also an associated anemia. Her upper lids were edematous. Grade iii retinopathy was apparent. There was engorgement of the veins of the neck, but I couldn't feel the thyroid. Her lungs had bilateral rales at both bases. Her heart was enlarged to the left with A-2 greater than P-2. During this admission I heard a Grade ii systolic murmur at the apex. Her abdomen was distended with shifting dullness. Her liver was palpable 3 to 4 fingerbreadths below the right costal margin, but I couldn't feel the spleen. She had 1+ pretibial edema. I could not perform a satisfactory pelvic examination because of a tight hymen.

On the last admission I was more impressed with her markedly edematous appearance. Her blood pressure was 160/100. Her eyebrows were very bristly and sparse; she had more edema of both upper and lower eyelids and she had edema of the bulbar conjunctiva. Her lungs at this time were clear. Her heart was enlarged to the left with a louder A-2 than P-2, but this time I heard no murmurs. Her rhythm was regular. This time the liver was not palpable and I could not unequivocally demonstrate shifting dullness. Her skin was very dry. My impression was that of myxedema, diabetes and hypertension with heart failure. I felt the anemia was due to blood loss, possibly due to her menorrhagia. I assumed she had diabetic renal disease because of the changes of the proteins and the marked electrolyte imbalance.

Myxedema Heart

In discussing myxedema of the heart, the first thing to stress is that it's a reversible heart disease. Although it isn't very common, you should be able to make the diagnosis if you think of it. In the literature it is stated that about 50% of the patients will present themselves with a "myxedema heart." The heart is enlarged across the chest both right and left, and has a globular appearance. The enlargement is thought to be due to 1) a pericardial effusion without pericarditis, and 2) probably an infiltration of the myocardium with the same myxomatous material that is found in the skin and in the muscles. These hearts do respond to thyroid therapy but thyroid should be given very cautiously in small increments of small doses of desiccated thyroid. It should also be stressed that therapy should be given orally.

Heart failure specifically due to primary myxedema heart is not common. When it does occur, it is usually associated with arteriosclerosis of the coronary vessels. It is common to find diffuse arteriosclerosis together with marked myxedema. In this case I have assumed that three factors in addition to the myxedema, namely, anemia, hypertension and primary arteriosclerosis of the coro-

nary vessels, are causally related to the heart failure.

Anginal symptoms are not uncommon in patients with myxedema and this is thought to be due to coronary sclerosis producing coronary insufficiency. The electrocardiogram in patients with myxedema may be classic with low voltage and with flattening or absence or inversion of T waves in all the leads. This pattern is said to be almost diagnostic of a myxedema heart. Digitalis by itself is not beneficial for primary myxedema of the heart. Patients do not usually respond to digitalis therapy alone but they do respond to thyroid therapy.

In myxedema there is a decrease in cardiac output as well as in circulation velocity and peripheral blood flow as well as in the total volume of blood. Nephrosis alone may also decrease blood volume. However, when a patient goes into failure for any cause there is usually an increase in plasma volume. In reviewing the laboratory work here you will note that this patient had a plasma volume that was increased over normal despite the fact that she had myxedema and nephrosis.

QUESTION (To Dr. Bernstein):

Are patients with myxedema unusually sensitive to morphine?

Dr. Bernstein:

Yes. The patients with myxedema are said to be very sensitive to morphine, but this patient did have acute pulmonary edema and obviously heroic measures were required. She did respond to morphine without being over-sedated. I saw her after she had received morphine and she was clinically improved. If I had it to do again, I would give her morphine, but very cautiously and in small dosage.

Dr. Leigh Rosenblum:

Patients with myxedema have an increased incidence of systolic and diastolic hypertension which is usually not marked. Occasionally, thyroid medication will reduce the blood pressure. This may be due to sodium diuresis. Reserpine decreases the BMR for some unknown reason. So, in a patient who is already myxedematous, I would be hesitant about using reserpine to control blood pressure.

Dr. Emanuel E. Mandel:

This patient presented evidence of renal disease in view of proteinuria, azotemia and abnormal findings in the urinary sediment, although no oval fat bodies and no casts were reported. At the time of the last admission, the serum albumin was depressed along with 4 plus proteinuria.

One has to consider that a patient with diabetes of at least 15 years' duration is likely to have one or more of the three renal disorders which constitute the triad of diabetic nephropathy, namely, diabetic glomerulosclerosis, pyelonephritis, and nephrosclerosis. The available evidence permits diagnosis only of the first mentioned lesion.

Renal Function in Myxedema

This patient also had myxedema, and renal function has been reported — both in experimental animals and in the human — to be impaired with diminished thyroid function. Some of the experimental data indicate a rapid decrease in glomular filtration and in maximal tubular resorption and tubular excretory capacity within a few days following thyroidectomy. This phenomenon has been related to: (1) a decrease in the renal blood flow, which coincides with Dr. Bernstein's remarks about a decrease in cardiac output and in peripheral blood flow, and (2) interference with the normal enzymatic transfer of substances across the renal tubular membrane. Decrease in renal blood flow reduces glomerular filtration as indicated by inulin clearance and other measurements. Glomerular filtration, as well as tubular transfer mechanisms, have been found in humans to respond to specific replacement treatment.

Aside from these aspects, a recent article reports a frequent increase in serum uric acid and decrease in urinary excretion of uric acid in patients with marked hypothyroidism. This change was apparently not correlated with an increase of other nitrogenous substances in the blood, for in most of the cases which

were studied, serum urea was in the normal range. The incidence of elevation of serum uric acid was greater among the male patients than among the females in this series. The elevation was attributed by the authors to a decrease in renal blood flow and to altered tubular transfer mechanisms, and was usually not associated with increase in the serum cholesterol level.

On the other hand, there has been some recent evidence indicating a frequent coincidence of (idiopathic or familial) hyperlipemia with hyperuricemia in the absence of disturbed renal function. Hence, the possibility may be considered of a more basic metabolic connection between fat metabolism and nucleoprotein metabolism than is generally recognized, and elevation of uric acid in the serum of myxedema patients may not be due to a renal factor exclusively. In this connection, I may also quote a report concerning a large group of gouty patients, of whom about 25% had both clinical and laboratory evidence of hypothyroidism. Thus, there is very distinct overlapping between hyperuricemia and hypothyroid features.

Aside from metabolic considerations, we know that the thyroid plays an important part in the development of the kidneys in the fetus. Thyroidectomy in the early intra-uterine life of rats and dogs inhibits the development of kidneys more than that of most other organs. However, athyroidism occurring after the kidney has fully developed causes no demonstrable histologic changes.

The Nephrotic Syndrome

As regards our patient's problem, she had evidence of a nephrotic syndrome manifested by proteinuria, hypoalbuminemia, hypercholesterolemia, peripheral edema and ascites. To what extent the impairment of her renal function may be due to her hypothyroidism is impossible to tell even histologically.

The nephrotic syndrome of diabetic glomerulosclerosis occurs so commonly in patients who also have edema due to heart failure that differential diagnosis is often a problem for the clinician. In this case, myxedema further complicates the picture. While pericardial effusion and non-pitting edema are common in myxedema, ascites is infrequent. Prompt response to cardiac therapy indicated that cardiac failure played some role in the disturbance of fluid balance observed in this patient. She had acute pulmonary edema manifested radiologically; combined treatment with digitalis, morphine and mercurial diuretics resulted in relatively rapid improvement. Nevertheless, the persistent proteinuria and low level of serum albumin even after her cardiac status had been stabilized strongly support the diagnosis of diabetic glomerulosclerosis. Additional quantitative measurements of urinary protein and more detailed study of the urinary sediment would have been of great help in definitely establishing the diagnosis.

There is an interesting aspect concerning sodium metabolism in this type of patient. In myxedema, in contrast to what occurs in congestive heart failure, water is retained and sodium is excreted very efficiently. Patients with heart failure retain sodium and water; the myxedematous patient retains water but may lose sodium even to the point of depletion. Basically, there seem to be different mechanisms involved.

Dr. Leigh Rosenblum:

The terminal events began 1 week after her final admission and followed repeated attacks of hypoglycemia. At this time she was in an unexplained obtunded state. The stupor was not due to diabetic acidosis or renal failure. Residual nervous system depression following hypoglycemia was not the cause, as her mental state deteriorated when she had not received insulin and had been receiving intravenous glucose.

At this time her temperature taken with a thermometer from the chemistry laboratory was 93.1°F. Since she was myxedematous, comatose and hypothermic with a normal blood pressure, it was correctly assumed that the criteria for "myxedema coma" were met.

What precipitated the myxedema coma in this patient? Cold, infection, trauma or other stress have all been implicated as precipitating agents and in this patient the hypoglycemic episodes might be considered the stress. The physiologic

and/or biochemical mechanisms responsible for myxedema coma are not completely understood but possible factors include: decreased cerebral blood flow; decreased glucose and oxygen uptake by the brain; and cerebral edema with increase in cerebrospinal fluid pressure. It is not noted in the protocol, but terminally she had massive retinal edema.

The serum electrolytes at this time were those usually seen in myxedema coma; that is, very low sodium and chloride. The mechanism responsible for these changes is not known. Adrenal insufficiency has been suggested but plasma glucocorticoids are normal in uncomplicated myxedema although urine glucocorticoids may be low. In the present case, the 24 hour urinary 17-hydrosteroids were normal. Other possibilities for the low sodium and chloride include water retention and diminished sweating in the presence of tissue destruction. In this patient the serum CO_2 was only slightly reduced. Patients with myxedema coma may have severe hypoventilation resulting in CO_2 retention and CO_2 narcosis which may necessitate tracheostomy and artificial respiration to reduce the CO_2 and increase oxygenation.

The prognosis of a patient with myxedema coma is poor, with almost all cases resulting in death. This patient was treated aggressively with oral triiodothyronine, hydrocortisone, a warming blanket and, later, intravenous T_4 when it became available. It is of interest that she improved remarkably for a short time only to relapse into coma unresponsive to all therapy. Since myxedema coma is uncommon and treatment usually unsuccessful, numerous regimens of therapy have been advocated.

Recommended dosage of thyroid hormone varies from minimal to massive amounts, for example, T_3 from 25 to 1000 mcg. daily. If large doses are administered and the patient responds, future dosage should be reduced to avoid precipitation of a myocardial infarction and other cardiovascular complications. Adrenal steroids are administered to avoid adrenal insufficiency which may complicate thyroid hormone therapy. Many thyroidologists recommend warming the hypothermic patient cautiously; however, some disagree and leave the patient hypothermic while instituting other therapy.

Therapy will probably only improve when we learn more about the pathophysiology of myxedema coma. Until that time we can only hope that hypothyroidism is recognized and treated before the stage of myxedema coma.

AUTOPSY FINDINGS

Dr. John Gruhn:

The body weighed 49 kgs. (108 lbs.) and measured 143 cms. (4 ft. 8 in.) in length.

There was a typical myxedema facies with swollen, waxy, pale skin, periorbital edema, deepening of the forehead and nasolabial folds, dry coarse eyebrows, and thin coarse hair on the scalp.

The abdomen was protuberant. There was no edema of the extremities.

On opening the body, 300 cc. of clear straw-colored fluid was found in the peritoneal cavity, 100 cc. of similar fluid was found in each pleural cavity, and 30 cc. was present in the pericardial sac.

The heart weighed 235 grams. The expected heart weight for this body weight is 235 grams. The heart was grossly normal in size, shape, contour, color and muscular turgor. Internal examination was completely unremarkable save for a minor amount of atherosclerosis along the posterior cusps of the valves. Multiple sections of the muscle demonstrated minimal areas of interstitial edema with the tiniest foci of fibrosis and a very minimal degree of coronary sclerosis.

There was a moderate degree of atherosclerosis of the aorta which is not different from what we would expect in a woman of 37.

Despite the clinical cardiac difficulties, no organic lesion was observed in the heart. When the group at the Massachusetts General Hospital reviewed all their cases they came to the conclusion that there was no specific lesion in the heart in myxedema that couldn't be attributed to atherosclerosis. Other authors, of course, have reported differently.

Another point of interest is whether atherosclerosis is actually more severe

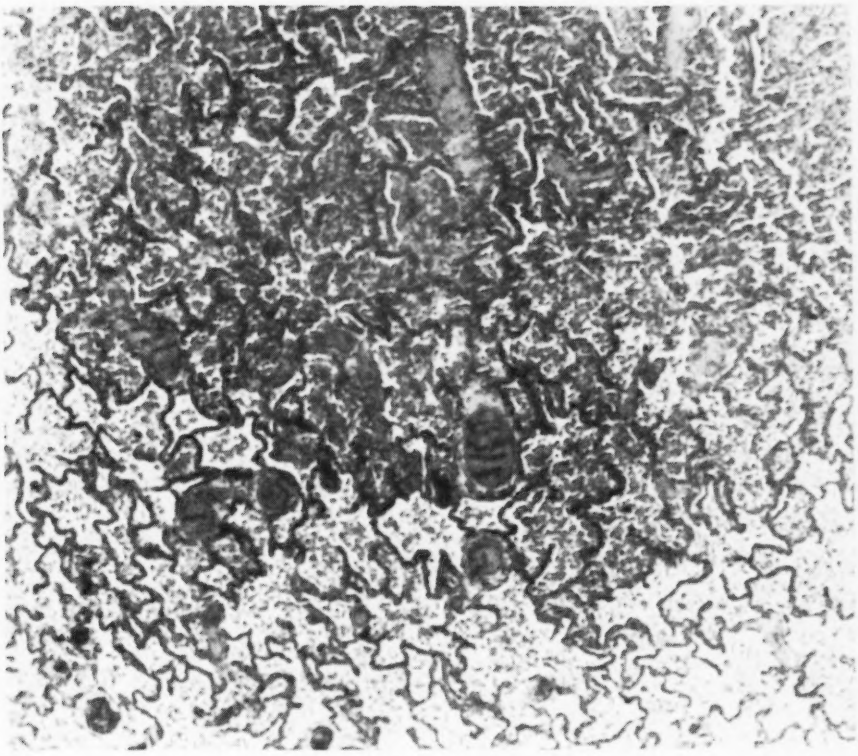

Fig. I. Focal bronchopneumonia.

in myxedema. One worker who has done very careful studies, Herman Blumgart, has treated angina in atherosclerotic heart disease by radioactive destruction of the thyroid, and has published his conclusion that hypothyroidism so induced does not exaggerate atherosclerosis. His point of view stands in contrast to what is commonly taught.

The lungs at autopsy were just slightly heavier than normal. There was a Ghon focus measuring 1.5 cm. as a result of ancient tuberculosis in the left upper lobe. The pleural surfaces were smooth and glistening. The lungs were darker, less crepitant than normal and in an occasional bronchus was slimy, purulent material. There was a terminal bronchopneumonic infiltrate, not very extensive but rather widely scattered.

The liver weighed 1500 grams and was normal grossly and microscopically. Franklin Hanger, who devised the cephalin flocculation test, reviewed all the autopsy material at the Columbia-Presbyterian Medical Center in New York and found no significant changes in liver function studies. Their pathologic anatomy section could find no characteristic or specific changes in the liver in myxedema cases either.

The spleen weighed 70 grams. It was normal.

The stomach was markedly dilated. The mucosal surface was coated with a great excess of mucus. The pyloric ring was so enormously edematous it was difficult to get a finger through into the duodenum. There was no hemorrhagic lesion within the stomach.

There was a source for bleeding in the esophagus. She had a terminal esophagitis with minimal focal ulceration of the esophagus with sparse cellular infiltra-

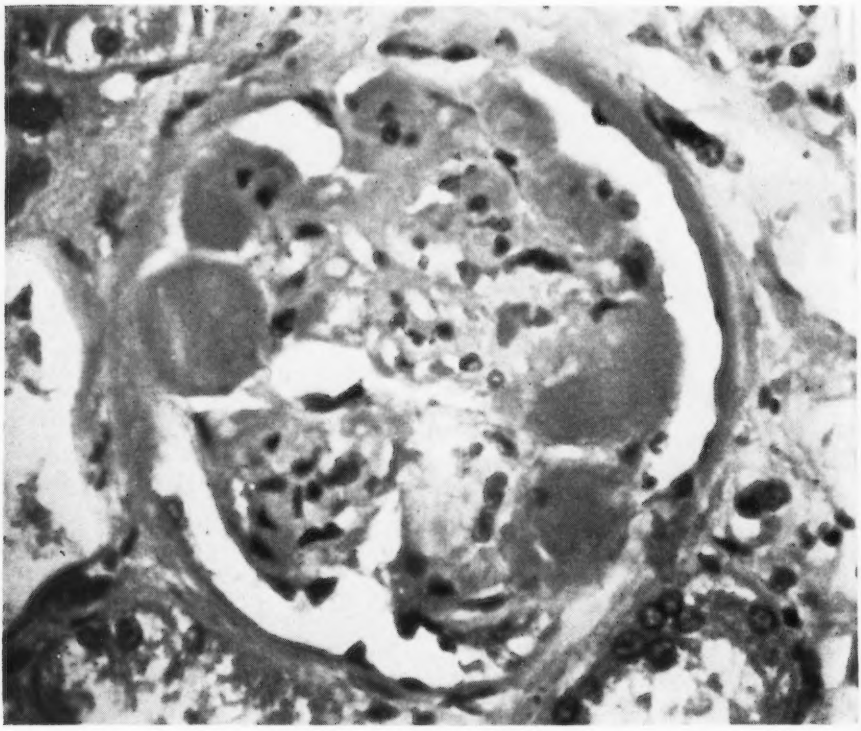

Fig. II. Diabetic nodular glomerulosclerosis.

tion and local vascular reaction. This was correlated with the vomiting and the intubation.

There was an enormous degree of submucosal edema of most of the G. I. tract. The special histochemical studies for mucopolysaccharides didn't stain any specific myxedema fluid.

There was also a benign adenomatous polyp in the colon.

The pancreas was grossly unremarkable. This woman was severely diabetic for at least 15 years but the pancreas was not fibrotic or fatty; grossly it looked like any normal pancreas. We have done no special histochemical studies with beta-granule technics but the islets appeared essentially unremarkable with the H & E stains. There was, however, a decrease in the number of islets.

The kidneys weighed 110 and 130 grams respectively. The external surfaces of the kidneys were relatively smooth. The main vessels were not notable. The ureters were unremarkable. The cut-sectioned surfaces were unremarkable. The small vessels did not stand out more prominently than usual. This patient had no gross pyelonephritis and no gross vascular changes. Her kidneys were not large, pale or swollen.

Most of the glomeruli of this patient were larger than normal. In many, if not most of them, were eccentric, peripherally placed, hyalinized rounded balls or nodules with a cluster of flattened nuclei at the periphery and sometimes a dilated capillary loop at the outer edge. The nodules did not involve the entire glomerulus; usually there was only one per glomerulus but occasionally there were several.

Silver stains demonstrated a characteristic laminar curleycue reticulin within the balls. Whenever the nodular lesions are present, the light microscopist also

finds a diffuse thickening of basement membranes which may be emphasized by P.A.S. stains. Sclerosis of small arteries was demonstrable. In a very rare glomerulus afferent and efferent arteriosclerosis was demonstrable.

Specificity of Renal Changes

There has been a long-standing debate whether the nodular lesion is specific for diabetes. This issue has finally been resolved in the affirmative. The only lesion which is really likely to require differential diagnosis by the pathologist is lobular glomerulonephritis. In this latter lesion, which is not specific for diabetes, usually every glomerulus is involved, there are multiple balls or nodules in every glomerulus, the nodules are not predominantly peripheral but may be centrally placed, the reticulin is disorganized rather than laminar, and an occasional crescent may be found in Bowman's capsule. The specificity of the nodular lesion is no longer debatable.

Although the nodular lesion is specific for diabetes, does it account for the symptomatology or correlate closely with the renal functional abnormalities? Robbins and his associates published a classical study in 1952 which demonstrated that the clinical syndrome of diabetic glomerulosclerosis can occur in the absence of the nodular lesion and that the nodular lesion can occur without the clinical syndrome. It is now an incontestable fact that the severity of the degree of histological glomerular involvement by nodules does **not** parallel the degree of severity of renal functional impairment. This suggests that another lesion is responsible for the glomerular dysfunction.

We have already mentioned the diffuse

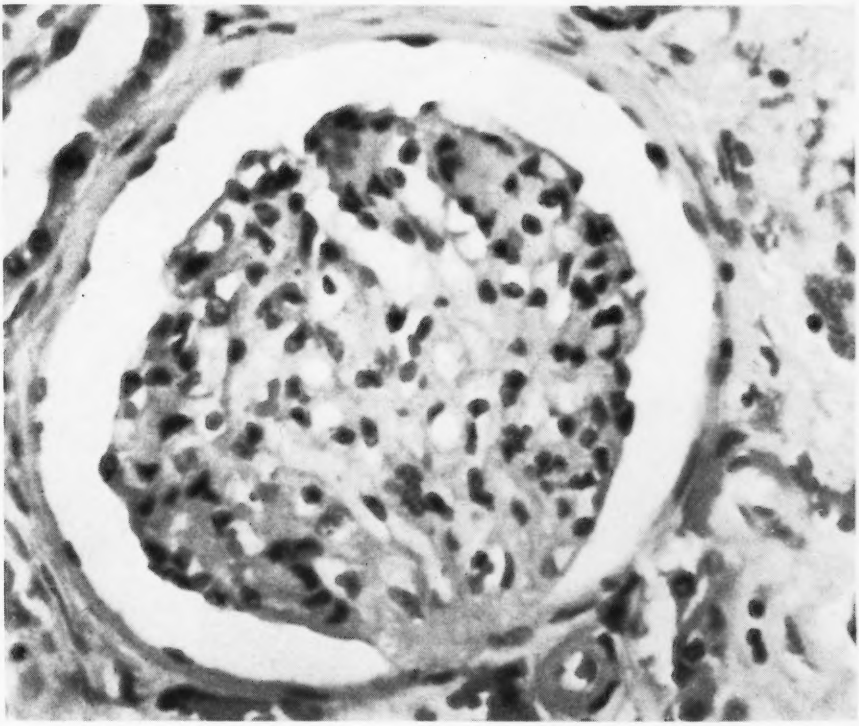

Fig. III. Diabetic diffuse glomerulosclerosis. There is also hyaline sclerosis of an arteriole to the right of the hilar root.

thickening of the glomerular basement membrane in this case. Only a few years ago it was considered futile to discuss the relationship of the diffuse lesion to the nodular lesion in diabetics. Before the era of the P.A.S. stain the diffuse lesion was generally ignored, regarded as non-specific or considered to be a consequence of arteriolar nephrosclerosis. It can generally be distinguished from the latter by several criteria. The diffuse diabetic lesion is more prominent at the periphery than at the hilar root, the involved glomeruli of diabetes tend to be larger than normal and there is neither a fibrillar appearance nor does the lesion contain collagen or reticulin. This diffuse lesion has been stressed because of its physiological and clinical relevance. It has been shown that the severity of the diffuse lesion can be correlated precisely with the severity of hypertension, proteinuria and renal failure and with the incidence of edema and the nephrotic syndrome.

The nodular lesion which has been historically associated with the clinical syndrome is not responsible for the physiologic derangement of renal function. The diffuse lesion is the morphologic basis for altered glomerular function.

The diffuse form of the glomerular lesion may occur alone but the nodular form never occurs without the diffuse form.

These lesions occur in a large number of diabetics. In the somewhat selective material of Kark, the diffuse form occurred in 75% of the cases and the nodular form in about 50%.

Routine autopsy material does not permit subtle histochemical and enzymatic

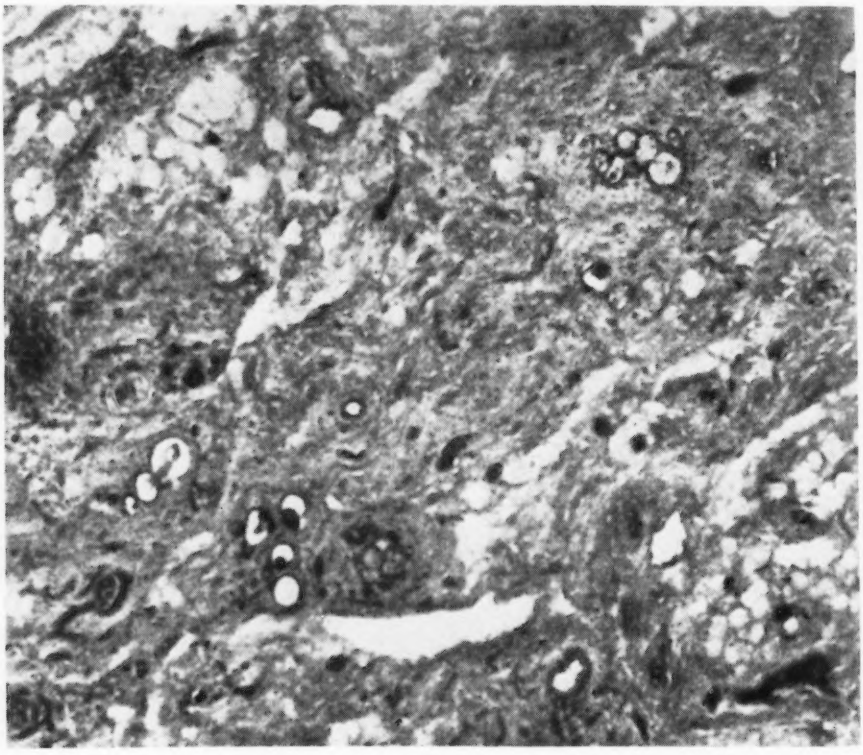

Fig. IV. Diffuse fibrosis of thyroid gland containing few residual follicles and sparse lymphocytic infiltrates.

studies which might be correlated with tubular function. But the Oil-Red-O fat stains on frozen sections of formalin fixed tissue in this case demonstrated marked deposition of lipid in tubules. If oval fat bodies had been repeatedly searched for in the urine, they would have been found.

Contribution of Electron Microscopy

The electron microscopist has contributed greatly to our appreciation of nephrosis and diabetic glomerulosclerosis. To understand this contribution we must consider two basic concepts. First, electron microscopy does more than magnify details. It permits greater resolution of detail than light microscopy by a factor of 250. Good light microscopes permit resolution of detail to 0.25 micra and magnification to about 1500 diameters. Electron microscopes permit resolution of detail to 10 Angstrom units (1A=.0001 micron) and magnification to 200,000 diameters. Second, it has taught us that the "basement membrane" of the light microscopist actually consists of three layers: the basement membrane (or lamina densa) itself, covered on the outside by foot processes from epithelial cells (the podocytes of the pedicles of the epithelial cells) and covered thinly on the inside by an extension of the endothelial cells (the lamina fenestrata or attenuare).

The first outstanding correlation of ultrastructure with pathologic renal function was the demonstration of altered foot processes in nephrotic syndromes. It was once thought that lesions of foot processes were the primary or sole ultrastructural basis of nephrosis. More re-

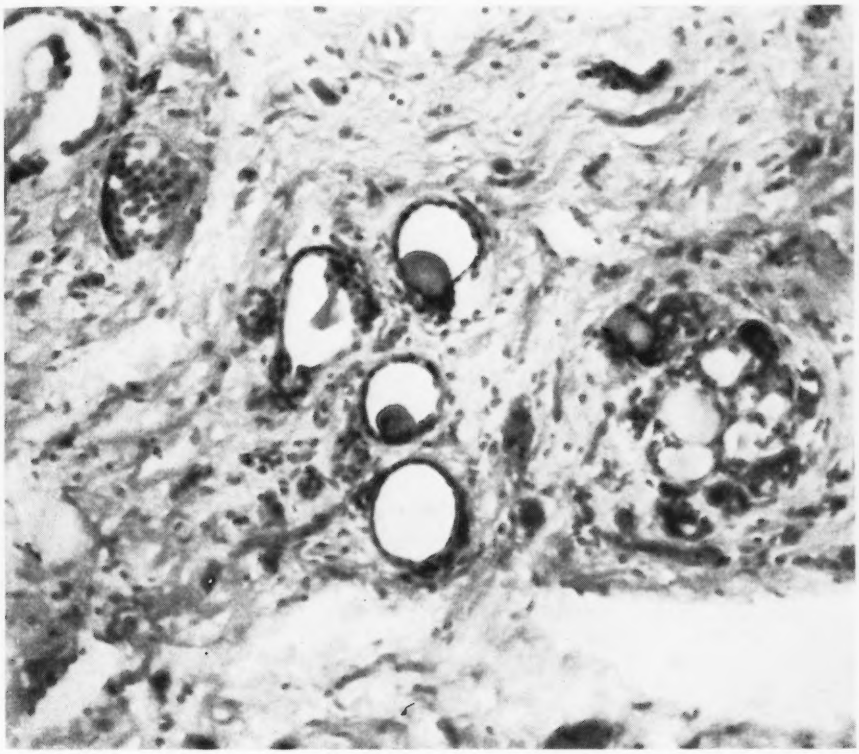

Fig. V. Residual thyroid follicles.

cently specific lesions of each of the three components of the "basement membrane" have been associated with experimental nephrotic states. It is becoming clearer that the three component system works as a single physiologic unit.

The electron microscopists have demonstrated that in diabetic glomerulosclerosis the true basement membrane (lamina densa) is increased from 2 to 10 times in thickness. The nodular masses appear to be material having the same tincture, texture and kind of material as the basement membrane (lamina densa). In electron micrographs it appears to come off the basement membrane and to infiltrate between endothelial cells.

The most important contributions of the electron microscopists go far beyond diagnostic considerations and are concerned with the ultrastructural basis of proteinuria, glomerular filtration mechanisms and associated problems.

According to most electron microscopists, the diabetic lesion is intracapillary, not intercapillary. Furthermore, the lesion is not a sclerosis, or in other words, that it is not a deposition of collagen, reticulin, collagenous or fibrous material. Our Department no longer uses the terms Kimmelstiel-Wilson lesion, syndrome or disease since the terms have been stretched elastically far beyond the original clinical and pathological descriptions. For the glomerular lesions themselves we use the terms diffuse and/or nodular diabetic glomerulosclerosis.

We did not study the peripheral nerves of this patient but we did study the spinal cord with care. Both diabetics and myxedema patients may have neuropathies and myopathies. In multiple sections of her entire cord we found normal myelination and no anatomic evidence of neurologic disease.

The ovaries weighed 12 grams each. A few small follicle cysts were seen but no corpora lutea were present. There was a rare persistent ovarian follicle. The ovarian stroma was edematous. There was a degree of atrophy which appeared more pronounced than is usual at age 37.

The uterus was minimally atrophic.

The adrenals weighed 8 and 9 grams respectively. They were externally normal. Cut sections demonstrated normal lipid deposition. Histologic sections demonstrated a normal pattern. The group at the Massachusetts General Hospital demonstrated that when the adrenal was intact the pituitary was intact and vice versa. The group with Werner has demonstrated four gradations of adrenal function. Since this patient had normal urinary ketosteroid and oxysteroid excretion and anatomically intact adrenals, I am certain that she could not have had pituitary myxedema.

Unfortunately, permission to examine the brain and pituitary was specifically denied.

The four parathyroids were normal.

The thyroid gland weighed 3 grams. This gland was a thin, rubbery, firm, tan-white, shield-shaped mass having none of the meaty, fleshy, red-orange-tan appearance of normal thyroid. On gross section, the thyroid was fibrotic.

Microscopically the bulk of the thyroid consisted of loose fibrous tissue. After diligent search it was possible to find residual thyroid follicles, somewhat variable in size, usually smaller than normal, lined by flattened epithelium and containing sparse amounts of pale colloid. Occasional lymphocytic aggregates were present. Rare small nests of squamous epithelial cells were also found.

Examination of the tongue and skin revealed no pathognomonic changes.

Bone marrow slides demonstrated mild depression of erythropoiesis.

PATHOLOGIC DIAGNOSES

1. Atrophy and fibrosis of thyroid gland (clinical myxedema). "Myxedema" of stomach and intestine.
2. Diffuse and nodular diabetic glomerulosclerosis (clinical nephrosis). Hydrothorax and hydroperitoneum.
3. Mild atherosclerosis of aorta.
4. Acute focal confluent bronchopneumonia with pulmonary congestion and edema. Acute erosive esophagitis.
5. Terminal myxedema coma (clinical).

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